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EVOLUTIONARY EPIDEMIOLOGY AND THE DYNAMICS OF ADAPTATION

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The mean fitness of a population, often equal to its growth rate, measures its level of adaptation to particular environmental conditions. A better understanding of the evolution of mean fitness could thus provide a natural link between evolution and demography. Yet, after the seminal work of Fisher and its renowned "fundamental theorem of natural selection," the dynamics of mean fitness has attracted little attention, and mostly from theoretical population geneticists. Here we analyze the dynamics of mean fitness in the context of host-parasite interactions. We illustrate the potential relevance of this analysis under different scenarios ranging from a simple situation in which a parasite evolves in a homogeneous host population to a more complex one with host-parasite coevolution. In each case, we contrast the effects of natural selection, recurrent mutations, and the change of the biotic environment, on the dynamics of adaptation. Decoupling these three components helps elucidate the interplay between evolutionary and ecological dynamics. In particular, it offers new perspectives on situations leading to evolutionary suicide. As mean fitness is an easily measurable quantity in microbial systems, this analysis provides new ways to track the dynamics of adaptation in experimental evolution and coevolution studies.

KEY WORDS: Adaptation, coevolution, epidemiology, Fisher's fundamental theorem, host-parasite.

Theoretical evolutionary epidemiology analyzes the population dynamics of parasites and their hosts, together with their evolutionary dynamics (Day and Proulx 2004; Day and Gandon 2006, 2007). Classically, the analysis of evolutionary dynamics focuses on phenotypic traits like virulence, transmission, and recovery rates (Day and Proulx 2004, Gandon and Day 2007). In contrast, we focus here on the evolutionary dynamics of mean host and parasite fitness. Because host and parasite population growth rates are directly governed by mean population fitness, this analysis provides a direct link between evolutionary and epidemiological dynamics. In particular we show how this direct link helps to better understand the effect of recurrent mutations and environmental change in situations leading to population extinction.

This analysis also provides a way to rephrase classical evolutionary epidemiology models in the broader context of Fisher's fundamental theorem of natural selection. This theorem states that "the rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time" (Fisher 1930). The validity of this theorem has been challenged in many situations in which evolution does not lead to the maximization of mean fitness (Moran 1964; Ewens 1969, 1989; Nagylaki 1992, 1993). Price (1972) showed this apparent lack of generality of Fisher's fundamental theorem comes from a misinterpretation of the theorem. The change in mean fitness $\bar{w}$, in the context of the environment e, between two points in time is (Price 1972; Frank and Slatkin 1992):

$$\Delta\bar{w} = \bar{w}'\big|\, e' - \bar{w}|\, e, \tag{1}$$

where the prime refers to the values of $\bar{w}$ and e at the next time point. It is particularly useful to partition the change in mean fitness in the following way (Frank and Slatkin 1992):

$$\begin{aligned}\Delta\bar{w} &= \left(\bar{w}'\big|\, e - \bar{w}|\, e\right) + \left(\bar{w}'\big|\, e' - \bar{w}'\big|\, e\right)\\ &= \Delta\bar{w}_{ns} + \Delta\bar{w}_{ec},\end{aligned} \tag{2}$$

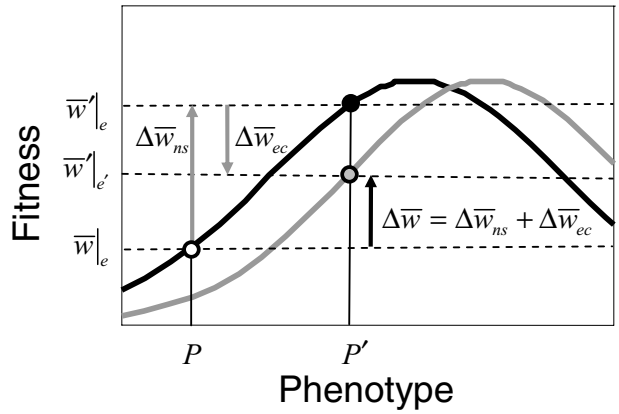

Figure 1. Decoupling the effect of natural selection and the change in the environment on mean fitness evolution. The black and gray curves are the fitness landscape at time t and $t + 1$, respectively, for a range of phenotypes. The white dot gives the value of the population phenotype and the associated mean fitness, at time t. The black dot gives the value of the population phenotype at time $t + 1$, and the associated mean fitness for the fitness landscape at time t. The gray dot gives the value of the population phenotype, and the associated mean fitness for the fitness landscape, both at time $t + 1$. Thus, the total change of mean fitness between time t and $t + 1$, is $\Delta\bar{w} = \Delta\bar{w}_{ns} + \Delta\bar{w}_{ec}$ and refers to the effect of natural selection at time t, $\Delta\bar{w}_{ns}$, and the degradation of the environment $\Delta\bar{w}_{ec}$.

where the first term, $\Delta\bar{w}_{ns}$, is solely due to the effect of natural selection, whereas the second term, $\Delta\bar{w}_{ec}$, refers to effect of the change of the environment, that is all the factors (biotic or abiotic) that may affect the fitness of genotypes (Fig. 1). This very general definition of the environment thus includes factors that may induce frequency-dependent or frequency-independent selection, and each factor may be viewed as one dimension of the environment (Mylius and Diekmann 1995). Price (1972) clarified Fisher's theorem by pointing out that it focuses only on $\Delta\bar{w}_{ns}$, and thus only on the partial change of mean fitness due to the action of natural selection. Yet, the complexity introduced by the change of the environment has rarely been used to understand the dynamics of adaptation in particular case studies. The dynamics of mean fitness is often studied in simplified ecological scenarios in which genotypic fitness do not vary with time (Ewens 1989), or vary very slowly (Nagylaki 1979, 1993). Typically, only the change of the environment due to density-dependence has been analyzed in any detail (Fisher 1930; Kimura 1958; Frank and Slatkin 1992; Nagylaki 1992).

In this article we analyze the dynamics of adaptation in the broader context of interspecific interactions, where the environment of a species depends on the abundance and evolution of other species. In particular we demonstrate its potential relevance in the study of host-parasite interactions. We use a general epidemiological model to describe both the host and the parasite dynamics. We explore the dynamics of mean fitness in a diversity of situations. First, when the parasite evolves in a homogeneous host population, the degradation of the environment of the parasite corresponds to the decrease of the density of susceptible hosts. Second, allowing the host to coevolve adds yet another factor to the degradation of parasite's environment. Those different case studies help to illustrate the different factors governing the dynamics of parasite adaptation. In particular, following and extending Price (1972), we show that the dynamics of adaptation can always be partitioned among the effects of (1) natural selection, (2) recurrent mutations, and (3) changes in the environment.

Epidemiological and Coevolutionary Dynamics

We use a classical SI model in which the host can either be susceptible (S) or infected (I). The total number of hosts is $H = S + I$ and the prevalence of the disease is denoted $\pi = I/H$. The rate of arrival of new susceptible hosts in the population (immigrants and newborns) typically depends on the number of susceptible and infected individuals, and is denoted $\theta(S, I)$ The rate of horizontal infection depends on the number of infected hosts and on the rate of horizontal transmission β of the parasites (the host population is assumed to be well mixed). Uninfected hosts have a mortality rate of δ, and infected hosts suffer extra mortality due to presence of the parasite (i.e., parasite virulence, α). Infected hosts may also recover with a per capita rate γ. We furthermore assume that, after recovery, the host becomes fully susceptible again. This yields the following set of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= \theta(S, I) - (\delta + \beta I)\, S + \gamma I \\
\frac{dI}{dt} &= \beta S I - (\delta + \alpha + \gamma) I \\
&= r I \\
\frac{dH}{dt} &= \theta(S, I) - (\delta + \alpha\pi)\, H \\
&= \rho H, \qquad (3)
\end{aligned}$$

where $r = (dI/dt)/I = \beta S - (\delta + \alpha + \gamma)$ is the per capita rate of change of the number of infected hosts, and $\rho = (dH/dt)/H = \theta(S, I)/H - (\delta + \alpha\pi)$ is the per capita rate of change of the total number of hosts (see Table 1 for main notations).

To model coevolutionary dynamics we extend the above epidemiological model (3) to incorporate multiple host variants and multiple parasite strains. The epidemiological parameters are then allowed to depend on both host and parasite characteristics. The production of new susceptible hosts, $\theta(S, I)$, is assumed to be a function of the host genotype only.

Table 1: Main notations used in the model.

Notations	Definitions
$S = \sum_j S_j$	Total density of uninfected hosts (sum over the different variants j of hosts).
$I = \sum_{i,j} I_{ij}$	Total density of infected hosts (sum over the different variants j of hosts, and the different strains i of parasites).
σ_{ij}	Probability of infection of host variant j, by parasite strain i.
$S_e^i = \sum_j \sigma_{ij} S_j$	Effective number of susceptible hosts from the perspective of parasite strain i.
p_i	Frequency of parasite strain i.
h_j	Frequency of host variant j.
$H = S + I$	Total density of hosts.
$\theta(S, I)$	Rate of production of new susceptible hosts.
δ	Host intrinsic mortality rate.
α	Parasite virulence (extra mortality).
γ	Host recovery rate.
r	Parasite population growth rate.
ρ	Host population growth rate.
Δr_{ns}, $\Delta\rho_{ns}$	Effect of natural selection on mean parasite and host fitness, respectively.
Δr_m, $\Delta\rho_m$	Effect of mutation on mean parasite and host fitness, respectively.
Δr_{ec}, $\Delta\rho_{ec}$	Effect of the change of the environment on mean parasite and host fitness, respectively.

In the following we use I_{ij} to denote the number of hosts of variant j that are infected with a parasite of strain i. Further, we use the notation $x_{\oplus j}$ and $x_{i\oplus}$ to denote the sum of x_{ij} over the index i and j, respectively. Thus, $I_{i\oplus} = \sum_j I_{ij}$ is the total number of hosts (of all variants) that are infected with a parasite of strain i, $I_{\oplus j} = \sum_i I_{ij}$ is the total number of hosts of variant j that are infected with any parasite, and we simplify notation by using $I = \sum_{ij} I_{ij}$, as the total number of infected hosts. Similarly, we define S_j as the total number of susceptible hosts of variant j, and $S = \sum_j S_j$ as the total number of susceptible hosts. It will also be convenient to define $H_j = I_{\oplus j} + S_j$ as the total number of hosts of variant j, and $H = \sum_j H_j$ as the total size of the host population.

For clarity of the results presented below we will also assume that new susceptible hosts arise through reproduction only (i.e., there is no immigration of hosts in the population), and therefore we replace $\theta(S, I)$ in the equation for the dynamics of S_j, with $b_j H_j(1 - \kappa H)$. This implies that births of susceptible hosts of variant j occur at a per capita rate of $b_j(1 - \kappa H)$, where the factor $(1 - \kappa H)$ incorporates a logistic-type of density dependence with parameter κ. Other assumptions about the rate of production of susceptible hosts, $\theta(S, I)$, can be handled in an analogous manner. Note that, in addition to these births, susceptible hosts are also produced through recovery of previously infected hosts.

In our general coevolution model the main traits involved in the interaction (probability of infection, transmission, virulence, recovery) are assumed to be governed by both host and parasite genotypes. In particular, σ_{ij} measures the probability of infection of host variant j, by parasite of strain i given that exposure occurs. Parasite transmission β_{ij} measures the production rate of parasite strain i when infecting a host of variant j. Similarly, α_{ij} and γ_{ij} measure the parasite-induced per capita mortality rate and the recovery rate, respectively, for a host variant j infected with a parasite of strain i.

Finally, we need to model the process by which genetic variability arises in both hosts and parasites. For the parasite, we assume all infected hosts contain only a single strain of parasite, but this strain type can change via mutation and within-host competition (Day and Proulx 2004; Day and Gandon 2006, 2007). This assumption relies on a separation of time scale argument, in which the outcome of the competition between two strains within a host is reached very quickly. We define μ_P as the rate at which such changes in parasite genotype within an infected host occur, and m_{ki}^P as the probability that, if such a change occurs in a host containing parasite strain k, it then becomes a host infected with parasite strain i. Thus the parameters μ_P and m_{ki}^P incorporate both parasite mutation and within-host competition. For the host population, we assume that newborn susceptible mutant individuals are produced by a host of variant k at a per capita rate $\mu_H b_k (1 - \kappa H)$, and these have mutated to host variant j with probability m_{kj}^H.

With the above specifications, a general model of the coevolutionary dynamics analogous to model (3) is

$$\frac{dS_j}{dt} = b_j H_j (1 - \kappa H) - \delta S_j - S_j \sum_{ik} \sigma_{ij}\beta_{ik} I_{ik} + \sum_i \gamma_{ij} I_{ij} + \mu_H \left(\sum_k m_{kj}^H b_k H_k - b_j H_j \right)(1 - \kappa H)$$

$$\frac{dI_{ij}}{dt} = \sigma_{ij} S_j \sum_k \beta_{ik} I_{ik} - (\delta + \alpha_{ij} + \gamma_{ij}) I_{ij} + \mu_P \sum_k \left(m_{ki}^P I_{kj} - I_{ij} \right). \quad (4)$$

Equation (4) give the evolutionary dynamics in terms of the numbers of each type, but it is sometimes more informative when modeling evolution to keep track of the frequency of each type, along with the total number of susceptible and infected hosts. Defining $p_i = \frac{I_{i\oplus}}{I}$ as the frequency of infections by parasite strain i, and $h_j = \frac{H_j}{H}$ as the frequency of hosts of variant j, we have

(Supporting Information Appendix S1)

$$\frac{\mathrm{d}p_i}{\mathrm{d}t} = p_i\,(r_{i\bullet} - r_{\bullet\bullet}) + \mu_P\left(\sum_k m^P_{ki}p_k - p_i\right) \tag{5a}$$

$$\frac{\mathrm{d}h_j}{\mathrm{d}t} = h_j(\rho_{\bullet j} - \rho_{\bullet\circ}) + \mu_{\mathrm{H}}\left(\sum_{\mathrm{k}} \mathrm{m}^{\mathrm{H}}_{\mathrm{kj}}\mathrm{b_k h_k} - \mathrm{b_j h_j}\right)(1 - \kappa \mathrm{H})\,. \tag{5b}$$

The subscript "•" indicates an average (over the corresponding index) across all infected hosts, whereas the subscript "○" indicates an average over the entire host population (susceptible and infected). For example, $x_{\bullet j}$ denotes the expectation of over the distribution $I_{ij}/I_{\oplus j}$, $x_{i\bullet}$ denotes the expectation of x_{ij} over the distribution $I_{ij}/I_{i\oplus}$, and $x_{\bullet\bullet}$ denotes the expectation of x_{ij} over the complete distribution I_{ij}/I. Also, denotes the expectation of x_{ij} over the distribution, H_j/H, and $x_{\bullet\circ}$ denotes the expectation of $x_{\bullet j}$ over the same distribution.

In equation (5), the quantities $r_{i\bullet}$ and $\rho_{\bullet j}$ are given by

$$r_{i\bullet} = \beta_{i\bullet}S^i_e - (\delta + \alpha_{i\bullet} + \gamma_{i\bullet}) \tag{6a}$$

$$\rho_{\bullet j} = b_j\,(1 - \kappa H) - \delta - \pi_j\alpha_{\bullet j}, \tag{6b}$$

where $S^i_e \equiv \sum_j \sigma_{ij}S_j$ denotes the effective number of susceptible hosts from the perspective of parasite strain i, and $\pi_{\ j} = I_{\oplus j}/H_j$ is the prevalence of infection among hosts of variant j. The quantity $r_{i\bullet}$ is the per capita rate of change of the number of hosts infected with parasite strain i, averaged over all host variants of the infected class. The quantity $\rho_{\bullet j}$ is the per capita rate of change of the total number of hosts of variant j, where infected hosts are averaged over all parasite strains. Those two quantities, $r_{i\bullet}$ and $\rho_{\bullet j}$, thus represent the fitness of parasite and host genotypes, respectively. Furthermore, we have

$$r_{\bullet\bullet} = (\beta S_e)_{\bullet\bullet} - (\delta + \alpha_{\bullet\bullet} + \gamma_{\bullet\bullet}) \tag{6c}$$

$$\rho_{\bullet\circ} = b_\circ\,(1 - \kappa H) - \delta - \alpha_{\bullet\bullet}\pi \tag{6d}$$

as the mean parasite and host fitness, respectively. Note that, in our model, the fitness of a genotype of a given species (6a and 6b) depends on the average life-history trait values of the focal genotype (i.e., parasite transmission and virulence, host fecundity) and on the resource level (i.e., the effective number of susceptible hosts for the parasite, the intensity of density dependence for the host). Hence, fitness may depend on the genotype frequencies of the interacting species (via the effect of the average phenotypic traits of the other species) but not on the frequencies of the other genotypes of the same species. Our model, however, could be readily extended to include this type of frequency dependence.

Equations (5) and (6) can be used to derive the rate of change of the average value of any trait, x_{ij} (e.g., σ, β, α, or γ). Day and Gandon (2006, 2007) focused on the situation in which the traits are governed only by parasite genotype (i.e., $x_{ij} = x_i$), and where the average parasite trait value is $x_\bullet = \sum_i p_i x_i$, which yields

$$\begin{aligned}\frac{\mathrm{d}x_\bullet}{\mathrm{d}t} &= \sum_i \frac{\mathrm{d}p_{\mathrm{i}}}{\mathrm{d}t}x_i \\ &= \sum_i (p_i x_i\,(r_{i\bullet} - r_{\bullet\bullet})) + \mu_P\left(\sum_{i,k} x_i m^P_{ki}p_k - x_\bullet\right) \\ &= \mathrm{cov}\,(x_i, r_{i\bullet}) + \mu_P\left(x^m_\bullet - x_\bullet\right),\end{aligned} \tag{7}$$

where $\mathrm{cov}\,(\mathrm{x_i}, \mathrm{r_{i\bullet}})$ is the covariance between the trait x and parasite fitness r over all parasite strains, whereas $x^m_\bullet = \sum_{i,k} x_i m^P_{ki}p_k$ is the average trait value of all mutations that arise (see Day and Gandon 2006, 2007). Similar equations can be obtained when the focal trait is governed only by the host, or by both the host and the parasite genotypes. The evolutionary dynamics of phenotypic traits under the control of the host and the parasite clearly deserves further attention (Restiff and Koella 2003; Grech et al. 2006; Day and Gandon 2007), but in this article we will not study the evolutionary dynamics of classical phenotypic traits (virulence, transmission, recovery. . .) but rather the dynamics of mean fitness itself.

Dynamics of Mean Fitness

Equations (5) and (6) can be used to derive the following results for the evolutionary dynamics of mean parasite and host fitness, $r_{\bullet\bullet}$ and $\rho_{\bullet\circ}$, respectively. Differentiating the expression for mean parasite fitness with respect to time, we obtain:

$$\frac{\mathrm{d}r_{\bullet\bullet}}{\mathrm{d}t} = \underbrace{\Delta r_{ns} + \Delta r_m}_{\sum_i \frac{\mathrm{d}p_i}{\mathrm{d}t} r_{i\bullet}} + \underbrace{\Delta r_{ec}}_{\sum_i p_i \frac{\mathrm{d}r_{i\bullet}}{\mathrm{d}t}} \tag{8a}$$

where, using equation (5a):

$$\begin{aligned}\Delta r_{ns} &= \sum_i p_i\,(r_{i\bullet} - r_{\bullet\bullet})\,r_{i\bullet} \\ &= \mathrm{var}\,(r_{i\bullet})\end{aligned} \tag{8b}$$

$$\begin{aligned}\Delta r_m &= \sum_i \mu_P\left(\sum_k m^P_{ki}p_k - p_i\right)r_{i\bullet} \\ &= \mu_P\left(r^m_{\bullet\bullet} - r_{\bullet\bullet}\right)\end{aligned} \tag{8c}$$

and, using (6a):

$$\begin{aligned}\Delta r_{ec} &= \sum_i p_i \frac{\mathrm{d}r_{i\bullet}}{\mathrm{d}t} \\ &= \sum_i p_i \frac{\mathrm{d}\beta_{i\bullet}}{\mathrm{d}t}S^i_e + \sum_i p_i\beta_{i\bullet}\frac{\mathrm{d}S^i_e}{\mathrm{d}t} - \sum_i p_i \frac{\mathrm{d}\alpha_{i\bullet}}{\mathrm{d}t} \\ &\quad - \sum_i p_i \frac{\mathrm{d}\gamma_{i\bullet}}{\mathrm{d}t}.\end{aligned} \tag{8d}$$

The quantities $\Delta\ r_{ns}$, $\Delta\ r_m$, and $\Delta\ r_{ec}$ refer to the effects of natural selection, recurrent mutations, and the change in the environment, respectively, on mean parasite fitness. They are analogous to $\Delta\bar{w}_{ns}$, $\Delta\bar{w}_m$, and $\Delta\bar{w}_{ec}$, respectively, in a discrete time model (see eq. 2 and Supporting Information Appendix S2). Equation (8b) shows that $\Delta\ r_{ns}$ is equal to the variance in fitness, and is thus always positive ($\Delta\ r_{ns} \geq 0$). In other words, natural selection tends to increase mean fitness. This increase in mean population fitness may be reduced by the effect of mutations whenever the average fitness of the mutants, $r^m_{\bullet\bullet} = \sum_k p_k \sum_i (m^P_{ki} r_{i\bullet})$, is lower than the average population fitness before mutation, $r^m{}_{\bullet\bullet} < r_{\bullet\bullet}$. Furthermore, as already noted by Fisher, the change in the environment (be it due to abiotic or biotic factors) may also contribute to the dynamics of mean fitness (Fig. 1). Near evolutionary equilibrium, the change in the environment will balance the positive effect of natural selection ($\Delta\ r_{ec} < 0$) and will thus result in a deterioration of the environment (Fisher 1930). Note that in many population-genetic models this environmental dependence of fitness is absent because $r_{i\bullet}$ is fixed (i.e., $\mathrm{d}\ r_{i\bullet}/\mathrm{d}\ t = 0$), and hence $\Delta\ r_{ec} = 0$. In our model the environment of the parasite is governed by the size and genetic composition of the host population (the parasite's resource), and $\Delta\ r_{ec}$ refers to the variation in mean parasite fitness due to changes in these aspects of the host population (8d). Host evolution results in changes in host variant frequencies, and consequently in modifications of the average transmission of each parasite strain (first term in 8d). Similarly, host evolution changes virulence and clearance rates (third and fourth terms). Host evolution also affects host susceptibility, σ_{ij}, thereby changing the effective number of susceptible hosts. Finally, changes in the number of uninfected host variants (epidemiological dynamics), also affect the effective number of susceptible hosts. Both of these latter factors account for the second term in (8d). Note that in our model we did not consider the potential direct effects of other parasite genotype frequencies on the fitness of the focal genotype. We do, however, consider the direct effects of the changes in host genotypes (coevolution) and the indirect effect of changes in other parasite genotype frequencies via the epidemiological dynamics. Adding the direct effects of changes in parasite genotype frequencies would not alter the general expression (8a) as these effects would be included as another dimension of the change of the environment (i.e., this would only add another term in 8d).

A similar analysis can be performed for the host. Differentiating the expression for mean host fitness with respect to time, we obtain:

$$\frac{\mathrm{d}\rho_{\bullet\circ}}{\mathrm{d}t} = \underbrace{\Delta\rho_{ns} + \Delta\rho_m}_{\sum_j \frac{\mathrm{d}h_j}{\mathrm{d}t}\rho_{\bullet j}} + \underbrace{\Delta\rho_{ec}}_{\sum_j h_j \frac{\mathrm{d}\rho_{\bullet j}}{\mathrm{d}t}}, \tag{9a}$$

where

$$\begin{aligned}
\Delta\rho_{ns} &= \sum_j h_j\,(\rho_{\bullet j} - \rho_{\bullet\circ})\,\rho_{\bullet j} \\
&= \mathrm{var}\,(\rho_{\bullet j}) \qquad (9b)\\
\Delta\rho_m &= \sum_j \mu_H \left(\sum_k m^H_{kj} b_k h_k - b_j h_j\right)(1-\kappa H)\,\rho_{\bullet j} \\
&= \mu_H\,(1-\kappa H)\left((b\rho)^m_{\bullet\circ} - (b\rho)_{\bullet\circ}\right) \qquad (9c)\\
\Delta\rho_{ec} &= \sum_j h_j \frac{\mathrm{d}\rho_{\bullet j}}{\mathrm{d}t} \\
&= b_\circ \frac{\mathrm{d}\,(1-\kappa H)}{\mathrm{d}t} - \sum_j h_j \frac{\mathrm{d}\pi_j \alpha_{\bullet j}}{\mathrm{d}t} \\
&= -b_\circ \kappa \frac{\mathrm{d}H}{\mathrm{d}t} - \sum_j h_j \alpha_{\bullet j} \frac{\mathrm{d}\pi_j}{\mathrm{d}t} - \sum_j h_j \pi_j \frac{\mathrm{d}\alpha_{\bullet j}}{\mathrm{d}t}. \qquad (9d)
\end{aligned}$$

The quantities $\Delta\ \rho_{ns}$, $\Delta\ \rho_m$, and $\Delta\ \rho_{ec}$ are the change in host mean fitness due to natural selection, recurrent mutations and environmental changes. As with parasite mean fitness, the direct effect of natural selection is to increase host mean fitness at a rate equal to the genetic variance in host fitness (9b). At the same time, however, host mutations may affect the dynamics whenever the average fitness of new mutants, $(b\rho)^m_{\bullet\circ} = \sum_k b_k h_k \sum_j (m^H_{kj}\rho_{\bullet j})$, is different to the mean fitness of juveniles in the absence of mutations, $(b\ \rho)_{\bullet\circ}$. Parasite evolution and epidemiological dynamics also result in changes in mean host fitness as displayed in equation (9d). The first term in (9d) reflects the impact of increased density dependence on birth rate when host population size increases (see also Fisher 1930; Kimura 1958; Frank and Slatkin 1992). The second term in (9d) accounts for the fact that the epidemiological dynamics can result in changes in the prevalence of the infection, and this will thereby affect host fitness because it affects the proportion of the population that suffers from infection. Finally, the third term in (9d) accounts for the fact that parasite evolution will alter the level of virulence experienced by hosts, and this too will affect the fitness of all host variants.

To better appreciate the significance of equations (8) and (9) and their interpretation, we consider some special cases that have been the subject of previous analyses.

NO HOST EVOLUTION

The simplest case occurs when only the parasite population harbors genetic variation. In this case all epidemiological parameters are a function of the parasite strain alone. Therefore we have $\rho_{\bullet j}$ being independent of j, $S^i_e \equiv \sigma_i S$, and $r_{i\bullet} = \beta_i \sigma_i S - (\delta + \alpha_i + \gamma_i)$. Equation (8) for the dynamics of mean parasite fitness then becomes $\frac{\mathrm{d}r_{\bullet\bullet}}{\mathrm{d}t} = \Delta r_{ns} + \Delta r_m + \Delta r_{ec}$, with:

$$\Delta r_{ns} = \mathrm{var}\,(r_i) \tag{10a}$$

$$\Delta r_m = \mu_P \left(r^m_\bullet - r_\bullet\right) \tag{10b}$$

$$\Delta r_{ec} = \frac{\mathrm{d}S}{\mathrm{d}t} E\left(\beta_i \sigma_i\right). \tag{10c}$$

Natural selection drives mean parasite fitness to larger values at a rate that is equal to the variance in parasite fitness. However, the recurrent production of maladapted parasite strains through mutation is likely to induce a mutational load (Haldane 1937). This is typically the case when mutations have only deleterious effects on fitness, as in classical quasi-species theory (Nowak 1992; Domingo et al. 2001; Bull et al. 2005; Day and Gandon 2006). More generally, mutations are likely to be drawn from distributions having both negative and positive effects on fitness. The geometric model of adaptation introduced by Fisher (1930) can be used to generate such distributions (Poon and Otto 2000; Martin and Lenormand 2006). This model assumes a single and fixed optimal phenotype, and the proportion of deleterious mutations depends on the distance of the mean phenotype to the optimal phenotype. In particular, when the population is near its optimal phenotype, most mutations are deleterious (i.e., $r^m{}_\bullet < r_\bullet$) and the net direct effect of mutation is to decrease mean fitness. Away, from the optimal phenotype, more adaptive mutants are generated, and this can speed up the dynamics of adaptation. In addition, an indirect effect of mutation is to increase the variance in fitness. This counteracts the direct effect described above, because it boosts the efficacy of selection. Thus a thorough evaluation of the impact of mutation requires a better understanding of its effect on both mean fitness and the variance in fitness (G. Martin and S. Gandon, unpubl. ms.).

The dynamics of mean fitness are not only driven by the balance between selection and mutation. The epidemiological dynamics may also affect mean fitness. Because parasite adaptations generally lead to a decrease in the number of uninfected hosts (i.e., $\frac{\mathrm{d}S}{\mathrm{d}t} < 0$), equation (10c) shows that epidemiological feedbacks will generally result in a deterioration of the environment for the parasite. Ultimately, the system may reach an evolutionary equilibrium in which these effects of natural selection, mutation, and epidemiology balance. Alternatively, in some situations, despite the positive effect of natural selection on adaptation (eq. 10a), the system may evolve toward extinction. First, this may occur because of the accumulation of deleterious mutation in the population (mutation threshold in quasi-species theory, Bull et al. 2007). Second, this may also occur because of a catastrophic decrease in the density of susceptible hosts (a drastic degradation of the environment) as a consequence of parasite adaptation.

To illustrate the latter scenario in which parasite evolution leads to the extinction of the whole system (evolutionary suicide), we consider another type of density dependence in the host. In particular, suppose the production of new susceptible hosts is $\theta(S, I) = bS^2(1 - S)$. This type of density dependence (modified from model eq 2 in Webb 2003) might arise if reproduction requires the interaction of two susceptible hosts (the S^2 factor) and it introduces a discontinuous transition to extinction in the host population (a necessary condition for evolutionary suicide to occur, Gyllenberg and Parvinen 2001). Figure 2 shows the joint epidemiological and evolutionary dynamics leading to both host and parasite extinction. We present results of numerical simulations (see Supporting Information) taking into account the epidemiological dynamics (eq. 3), mutations on the transmission rate of the parasite, and natural selection acting on the parasite only (the host population is assumed to be monomorphic). The decomposition of the dynamics of mean fitness into different components (Fig. 2C and eq. 10) clarifies the reasons why natural selection leads to deterministic extinction in this case. The direct effect of natural selection is to increase mean fitness, but the evolution of higher transmission rates feeds back on the dynamics of the host population through the reduction in the density of susceptibles, and indirectly affects the dynamics of mean fitness. At some point, the transmission rate crosses a threshold above which the host population cannot sustain itself, and the host population crashes. This change of the parasite's environment overwhelms the effect of natural selection and leads to parasite extinction. In a broader context, we believe this kind of analysis will allow one to pinpoint the factors responsible for evolutionary suicide and provide some general insights into the dynamics of Darwinian extinctions (Webb 2003).

HOST AND PARASITE COEVOLUTION

In the following we will contrast coevolution models with or without genotype-by-genotype (G × G) interactions between the parasite and its host (i.e., specificity). We first focus on a model analyzed by van Baalen (1998) where the host recovery rate may coevolve with parasite virulence. In this model, recovery is governed by host genotype whereas virulence and transmission are governed by parasite genotypes. In contrast, in the second type of coevolutionary models, infectivity is jointly governed by host and parasite genotypes (i.e., G × G interaction).

Coevolution without specificity

We first analyze the dynamics of parasite mean fitness in the model of van Baalen (1998) on the coevolution between parasite virulence and host recovery. In this model the host and parasite life cycles are very similar to the one assumed in the previous section except that mutations in the host may alter recovery rate and, as a consequence, the rate of reproduction (i.e., hosts with higher recovery rates are assumed to reproduce less: $\mathrm{cov}(\gamma_j, b_j) < 0$).

In this case we have $S^i_e \equiv \sigma_i S$ and parasite and host expected fitness are given by $r_{i\bullet} = \beta_i \sigma_i S - (\delta + \alpha_{i\bullet} + \gamma_{i\bullet})$ and

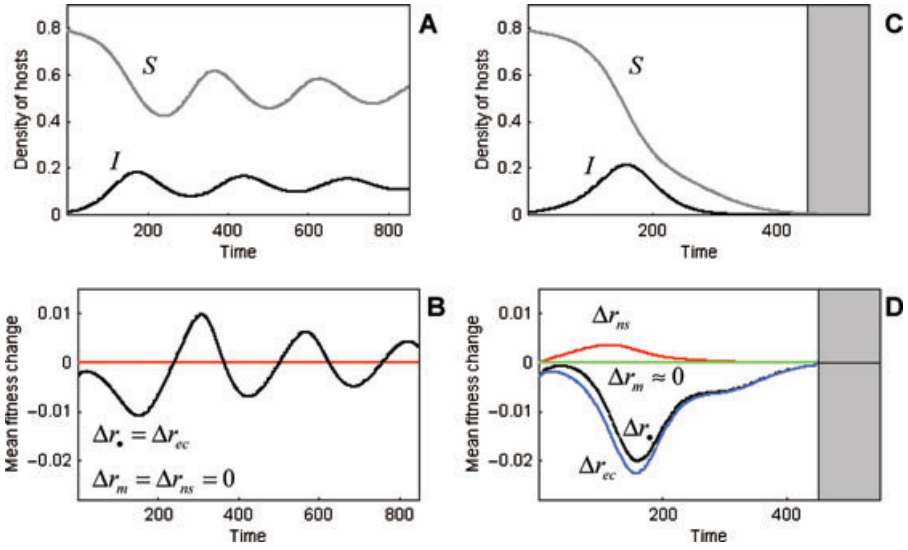

Figure 2. **Epidemiological dynamics (numerical simulations) with or without parasite evolution. In (A) and (C) we plot the dynamics of uninfected hosts, *S*(*t*) (gray line), and infected hosts, *I* (*t*) (black), over time. In (B) and (D) we plot the change in mean parasite fitness, $\Delta r_{\bullet}$ (black), and distinguish the effects of natural selection, Δr_{ns} (red), mutation, Δr_m(green), and the environmental change, Δr_{ec} (blue) on the dynamics of parasite adaptation. In (A) and (B) there is no parasite evolution (i.e., the mutation rate of the parasite population is set to zero). The host-parasite system slowly reaches an endemic equilibrium (A). Without mutation the dynamics of adaptation is fully governed by the change of the environment (i.e., $\Delta r_m = \Delta r_{ns} = 0$ and $\Delta r_{\bullet} = \Delta r_{ec}$). In (C) and (D) some parasite mutation is allowed to affect the transmission rate of the parasite. The evolution of the parasite toward higher transmission rates drives the host density to lower levels, and beyond the threshold density below which the host population goes extinct (C). Decoupling the effects of natural selection and of the change of the environment helps understand the evolutionary suicide of the parasite. The effect of mutation does not appear in (D) because its effect remains small in comparison with the effect of the environmental change. (D) shows that, in spite of the beneficial effect of natural selection on parasite adaptation, it is the degradation of the environment consecutive to the evolution of parasite transmission that explains parasite extinction. See main text and Supporting Information Appendix S4 for more details on the simulation model.**

$\rho_{\bullet j} = b_j(1-\kappa H) - \delta - \pi_j \alpha_{\bullet j}$, respectively. Thus, parasite mean fitness changes according to $\frac{dr_{\bullet\bullet}}{dt} = \Delta r_{ns} + \Delta r_m + \Delta r_{ec}$, with:

$$\Delta r_{ns} = \mathrm{var}\,(r_{i\bullet}) \tag{11a}$$

$$\Delta r_m = \mu_P \left(r^m_{\bullet\bullet} - r_{\bullet\bullet}\right) \tag{11b}$$

$$\Delta r_{ec} = \frac{dS}{dt} E\,(\beta_i \sigma_i) - \sum_i p_i \frac{d\gamma_{i\bullet}}{dt}. \tag{11c}$$

The only difference between equation (11) and equation (10) is the effect of host recovery rate evolution. Host coevolution is yet another component of the degradation of the environment of the parasite. An increase in the average recovery rate of hosts infected with strain i, $\gamma_{i\bullet}$, decreases the amount of host resource available for this particular parasite strain. The final term in (11c) sums the contribution of the degradation of the environment due to host coevolution for each parasite strain, over the strain frequency distribution. This term can also be expanded as

$$-\sum_i p_i \frac{d\gamma_{i\bullet}}{dt} = E\left(\mathrm{var}_i(\gamma_j)\right) - E\left(\beta_i S(\gamma_S - \gamma_{i\bullet})\right), \tag{12}$$

where, γ_S is the average recovery rate among uninfected hosts. This expression allows one to distinguish two main effects. The first term on the right-hand side of (12) is always positive as long as there is genetic variation in recovery rate among hosts infected by some parasite strain i (i.e., $\mathrm{var}_i(\gamma_j) > 0$). This variation allows for evolutionary change in the host population, from the perspective of strain i. Host variants with high recovery tend to be lost from the infected pool of hosts at a rate given by this variance. This has a beneficial effect on the environment of the parasite because it reduces the average recovery rate of infected hosts. In contrast, the second term on the right-hand side of (12) generally leads to a deterioration of the parasite's environment. This term depends on the difference between the mean recovery rate of uninfected and infected hosts, which tends to be positive because hosts with high recovery rates remain infected for a shorter period than hosts with low recovery rates.

To push the analysis of this model further we need to follow the evolutionary dynamics of recovery among infected and uninfected hosts. We forgo this derivation here because our focus is on the dynamics of mean fitness. This type of analysis could be used, however, to determine the evolutionarily stable host recovery rate

(by solving $d\gamma_{\bullet\circ}/dt = 0$). Under the simplifying assumption that the variance in virulence is negligible, we then obtain the same condition for evolutionary stability as van Baalen (1998). This is not surprising because the analysis of recovery evolution in van Baalen (1998) effectively assumed the parasite population to be monomorphic. The strength of our approach comes from the possibility of tracking coevolutionary dynamics (1) when both the host and the parasite populations are simultaneously polymorphic, and (2) away from the endemic equilibrium. It also more clearly illustrates the selective forces affecting the evolution of host recovery rates (i.e., the role of density dependence, the covariance between recovery and prevalence).

Coevolution with specificity

Next, we analyze the dynamics of adaptation in coevolutionary models with specificity. For simplicity, we will assume specificity to act only on σ_{ij}, the probability of infection of host variant j, by parasite strain i, given that exposure occurs. If we further assume that no variation occurs on the other host and parasite traits (i.e., $\alpha_{ij} = \alpha$, $\beta_{ij} = \beta$, $\gamma_{ij} = \gamma$, $b_j = b$), the changes in parasite and host fitness due to the variations of the environment (8c and 9c, respectively), reduce to:

$$\Delta r_{ec} = \beta \sum_i p_i \frac{dS_e^i}{dt} \tag{13a}$$

$$\Delta \rho_{ec} = -b\kappa \frac{dH}{dt} - \alpha \sum_j h_j \frac{d\pi_j}{dt}. \tag{13b}$$

Our general model allows one to combine epidemiological and coevolutionary dynamics. Yet in the following we further simplify the analysis of this model by assuming that the population sizes of the host and the parasite are fixed. In this case, the degradation of the environment is only governed by coevolution with the interacting species. In particular, the first term in (13b), which measures the effect of the change in host population size on the degradation of the environment of the parasite, vanishes. We also focus on a discrete-time version of the model so as to facilitate the occurrence of coevolutionary cycles in host and parasite genotype frequencies. The analysis of the dynamics of mean fitness in discrete time is presented in detail in Appendix S2 for a simple host-parasite model in which only the parasite is evolving (see section 2.1).

We will illustrate the resulting evolutionary dynamics under two contrasting scenarios. In the first, we assume infection is only possible when the host and the parasite have the matching genotype

$$\sigma_{ij} \begin{cases} = 1, & \text{if} \quad i = j \\ = 0, & \text{if} \quad i \neq j \end{cases}. \tag{14a}$$

Thus, in this model there is no intrinsic hierarchy among the different variants. Their relative fitness depend only on the composition of the host population. The negative frequency dependence selection induced by this model leads to typical "fluctuating selection" dynamics, with oscillations of host and parasite genotype frequencies.

In contrast, in the second scenario we assume that a parasite variant i is intrinsically fitter than a variant j, if $i > j$

$$\sigma_{ij} \begin{cases} = 1, & \text{if} \quad i > j \\ = 0, & \text{if} \quad i \leq j \end{cases}. \tag{14b}$$

This model leads to an "arms race" where both the host and the parasite evolve toward higher values of the trait governing specificity. These two models of specificity represent two extreme models of coevolution (Woolhouse et al. 2002). Hence, both are not very realistic: the first model assumes strict specificity and no costs of resistance, and the second relies on a very large number of genotypes to feed the "arms race" between the host and the parasite. These models, however, have heuristic value. They generate very different coevolutionary dynamics and lead to contrasting patterns of adaptation across time. The exploration of alternative models that may fall in between these two extreme cases clearly deserves more investigation (Agrawal and Lively 2002).

Figure 3 presents the evolutionary dynamics of parasite mean fitness under these two models. In both cases mean fitness oscillates around some equilibrium value (Fig. 3A,B). This equilibrium results from a balance between natural selection (increasing mean fitness), and the degradation of the environment (decreasing mean fitness) due to the coevolution of the interacting species. Thus, if the traits under selection are unknown it will be hard to distinguish between the two alternative models of specificity from the examination of the dynamics of mean fitness alone. This is due to the fact that, following mean fitness through time allows both the focal population and the environment (the interacting species) to change.

One way to disentangle the effect of natural selection and the degradation of the environment is to hold one of these factors constant and measure mean fitness across time points. That is, measure the mean fitness of a parasite population at time t against a host population at time $t + \tau$, where τ measures the time lag between the host and the parasite populations (i.e., the distance in time between the samples). When, $\tau = 0$ the host and the parasite populations are contemporaneous, whereas a positive (negative) value of τ means the host population is younger (older) than the parasite population. Thus, varying τ allows one to follow the change in the environment of the parasite only. When, τ is small (i.e., $|\tau| < 10$) the mean parasite fitness decreases with τ in both models (see the gray area in Fig. 3C,D). This illustrates the degradation of the environment induced by host coevolution.

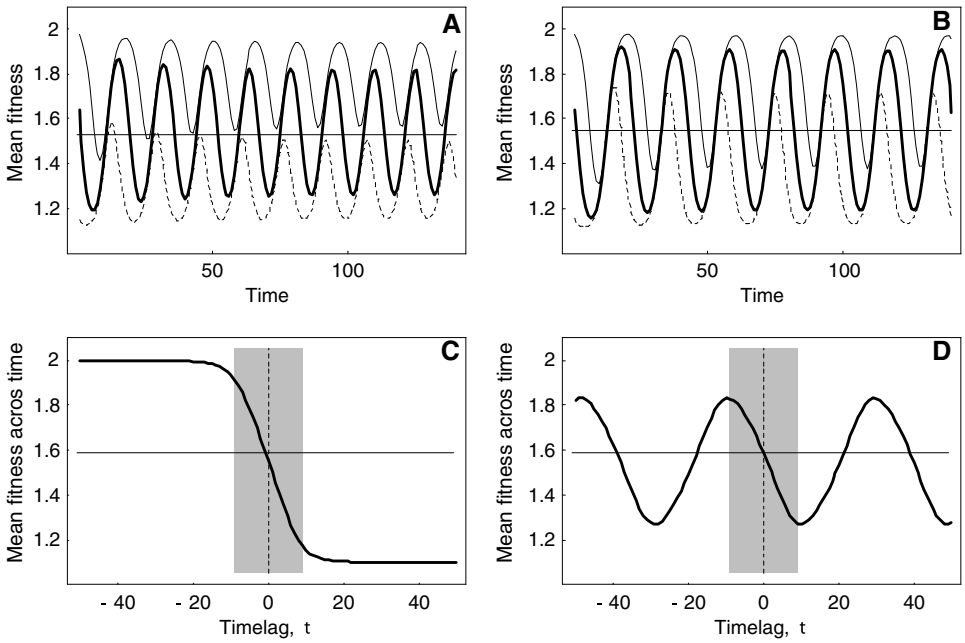

Figure 3. Dynamics of parasite adaptation in two coevolution models: in (A) and (C) the "arms race" model (eqs. 12b), and in (B) and (D) the "fluctuating selection" model (eq. 12a). In (A) and (B) we plot mean parasite fitness over time with contemporaneous hosts (bold line, $\tau = 0$), hosts from five generations in the past (thin line, $\tau = -5$), or five generations in the future (dashed line, $\tau = 5$). Similar plots can be constructed for any time lag, τ. Average parasite fitness (over 100 generations) can also be calculated for each time lag τ (e.g., [A] it is ~1.7 for the thin line [$\tau = -5$] and ~1.45 for the dashed line [$\tau = 5$]). These averages are plotted across a range of positive and negative values of τ in (C) and (D). In the gray area the time lag, τ, is small (i.e., $|\tau| < 10$). In the "arms race" we assume a large number of alleles in both the host and the parasite loci to prevent the coevolution to run out of diversity. In the "red queen" model, we assume specificity to be governed by a diallelic locus in both the host and the parasite. The polymorphism is maintained by negative frequency dependence. Parameter values: $\beta = 1$, $\alpha = 0.5$, $\mu_P = \mu_H = 10^{-3}$.

Interestingly, however, when τ is large, the two coevolutionary models behave very differently. In the first model (fluctuating selection dynamics) the mean fitness of the parasite oscillates with τ (Fig. 3C), whereas in the second one (arms race dynamics) parasite mean fitness is a monotonous decreasing function of τ (Fig. 3D). This suggests a potential route for inferring important information regarding the specificity of the host-parasite interaction using measures of parasite mean fitness in different environments.

Discussion

"Natural selection is not evolution" (Fisher 1930). The corollary of this famous quote is that evolution, and in particular the evolution of adaptation (i.e., mean fitness dynamics), is not solely driven by natural selection. First, recurrent mutations can strongly affect the dynamics of mean fitness. Second, the biotic and abiotic components of the environment in which organisms live and reproduce are also dynamical variables. These changes of the environment can have a huge impact on fitness, and consequently on the dynamics of adaptation. In the context of interspecific interactions, this environmental change is often referred to with the metaphor of the "red queen" (van Valen 1973). It is the constant degradation of the biotic component of the environment that explains why "it takes all the running you can do, to keep in the same place." This metaphor has been extremely useful for evolutionary biologists to capture the peculiarity of coevolutionary dynamics.

The effect of the "environment" on evolutionary dynamics, and ecological feedbacks, is also at the core of the adaptive dynamics framework (Dieckmann et al. 1999). In contrast to the approach presented here, however, adaptive dynamics is based on the simplifying assumption that mutations are rare. This assumption implies a decoupling of ecological and evolutionary time scales, and justifies an evolutionary analysis based on the invasion fitness of rare mutants (Waxman and Gavrilets 2005). Specifically, such models assume that the ecological/epidemiological dynamics of the population attain their asymptotic behavior before the appearance of a new mutant. As a result, such models essentially treat the dynamical change of the environment as occurring instantaneously. There can be multiple pathways (i.e., dimensions) through which the environment impinges on the fitness of a focal genotype, analogous to the multiple terms presented above in the decomposition of the environmental change (Mylius and Diekmann 1995). But the key difference in the adaptive

dynamics approach is that these feedbacks occur on a timescale that is faster than those of the component of change due to natural selection.

Both the approach presented here, and the adaptive dynamics approach each have their strengths, and we do not suggest that one is inherently better than the other. The strength of the adaptive dynamics approach is that it can greatly simplify the mathematical analysis, particularly if one is primarily interested in the long-term evolutionary equilibrium. Conversely, the approach presented here does not employ a separation of timescales and thus is more suited to examining the actual dynamics of evolutionary change, particularly if one is interested in the dynamics of mean fitness, because it explicitly deals with the evolutionary dynamics of polymorphic populations and decouples the effects of multiple factors on this dynamics (natural selection, recurrent mutations, change of the environment). In fact, this approach can be viewed as bridging the gap between population-genetic models based on the classical continuum-of-alleles (Crow and Kimura 1964; Lande 1980), which often assume very simple fixed fitness landscapes, and adaptive dynamics models, which incorporate realistic environmental feed backs at the expense of making restrictive assumptions about the mutation process.

DECOUPLING THE EFFECTS OF NATURAL SELECTION, MUTATION, AND ENVIRONMENTAL CHANGE

Following Price (1972), a key step in our analysis is the distinction we make between the effects of natural selection, of recurrent mutations, and of the environmental change (the change of fitness of the genotypes of the focal species) on the dynamics of adaptation. The positive effect of natural selection on mean fitness may be counteracted by the change of the environment and/or recurrent mutations.

In the absence of host evolution we showed that the degradation of the environment driven by the epidemiological dynamics can have dramatic effects on parasite adaptation and persistence. Although natural selection favors the most successful strategies, the indirect negative consequences of this evolution on the environment can overwhelm the dynamics of adaptation and lead the parasite population toward extinction. The decoupling of the effect of natural selection and the degradation of the environment can be extended to other situations in which Darwinian extinctions occur as well (Webb 2003). Population extinctions may also occur in the absence of any change of the environment if the recurrent introduction of deleterious mutations becomes very high. This is particularly likely in organisms such as RNA viruses with very high mutation rates that can be further increased by mutagens (Bull et al. 2005, 2007). The impact of mutation rates on the dynamics of adaptation, and on lethal mutagenesis (i.e., mutation driven extinctions), will be explored in a subsequent publication (G. Martin and S. Gandon, unpubl. ms.).

Another interesting situation is the evolutionary dynamics of parasites driven by host immunity. In this case the host population does not evolve genetically, but rather it changes immunologically through acquired immunity (Gill and Murphy 1976; Smith et al. 2004). This process is known to generate antigenic drift and immune escape in influenza. Boni et al. (2006) formalized this evolution during a single epidemic. Rephrasing their model (eq 37 in Boni et al. 2006) using our notation yields (Supporting Information Appendix S3)

$$\frac{\mathrm{d}r_{\bullet\bullet}}{\mathrm{d}t} = \underbrace{\mathrm{var}\,(r_{i\bullet})}_{\Delta r_{ns}} + \underbrace{\mu\beta S\,(1-\tau_1)}_{\Delta r_m} + \underbrace{\beta \sum_i p_i \frac{\mathrm{d}S_e^i}{\mathrm{d}t}}_{\Delta r_{ec}}. \qquad (15)$$

In this model, mutation allows the parasite to escape immune recognition. The parameter τ_1 measures the decrease in cross immunity arising from a single mutation. In contrast with models discussed above, mutation here has a beneficial effect on the dynamics of mean fitness. Thus, the first two terms in the right-hand side of (15) are both always positive. The third term, $\beta \sum_i p_i \frac{\mathrm{d}S_e^i}{\mathrm{d}t}$, accounts for the change in the environment of the parasite. In this model, the effective number of susceptible hosts is a monotonic decreasing function of time due to the lack of immigration of naïve hosts, and the fact that recovered hosts cannot be reinfected within the same season. In this case $\Delta r_{ec} < 0$ and this ultimately overwhelms the effects of natural selection and mutation, making $r_{\bullet\bullet} < 0$, and leading to the end of the epidemic.

In contrast with many coevolution models that rely on the simplifying assumption that host and parasite populations are fixed, our general evolutionary epidemiology framework (eqs. 4) allows population sizes to fluctuate. Host-parasite coevolution thus feeds back on the epidemiological dynamics, and vice versa. The exploration of the interplay between epidemiology and coevolution deserves further theoretical attention. This approach offers new avenues of research and in particular on the potential impact of coevolution on the growth rate of the parasite population. This may have very concrete implications in the context of chronic infections. For example, the within-host evolution of HIV virus has been invoked to explain the rate of progression toward AIDS (Nowak and May 2000). Focusing on the mean fitness of the virus population and decoupling the effect of natural selection and the degradation of the environment may shed a new light on this dynamics. There are two main components of the degradation of the environment. First, the depletion of HIV resources (human CD4 T-cells), which also measures the severity of the infection for the host. Second, the adaptive immune system of the host generates new lineages of specific immune cells that help contain the growth of the virus population. Throughout the infection, within-host evolution of HIV population counteracts both components of the degradation of the environment: increased replicative

fitness allows a more efficient exploitation of human T cells, and escape mutants can also cope with the "coevolving" immune system. During the asymptomatic phase of the infection, which may last several years, the degradation of the environment is balanced by the adaptation of the virus and results in a net zero growth rate of HIV (Arien et al. 2007). Disease progression then results from a perturbation of this balance. At some point, the adaptation of the virus overwhelms the degradation of the environment, the HIV density skyrockets, and this then ultimately degrades the environment even further, causing the host to become very sick. Decoupling the effect of natural selection and the effects of several factors of the environment (depletion of CD4 T cell counts, host adaptive immune system) may help better understand the variability in the rates of disease progression and to sort out current disagreement over the significance of HIV fitness in disease (Arts and Quiñones-Mateu 2003).

The approach presented in this article could also be generalized to other interactions between two evolving organisms. For example, the coevolution between males and females in sexual selection models, the nuclear-cytoplamic conflicts, or mutualistic interactions (Day et al. 2008). This would help reformulate these models in a proper ecological context. In a more general perspective decoupling evolutionary changes (changes in genotypes frequencies due to selection and mutation) and environmental changes helps clarify the dynamics of adaptation, or reformulate classical evolutionary problems.

Another classical evolutionary problem is the evolution of cooperation. If there is a cost of being altruist to your neighbors, how can natural selection promote this behavior? Kin selection theory demonstrates that cooperation may evolve if individuals interact preferentially with related individuals (Hamilton 1964). The direct fitness method (Taylor and Frank 1996) allows one to formalize this problem by distinguishing the direct effect of a focal individual on himself, with the effects of the interacting individuals. The effects of the other individuals in the population and their relatedness with the focal individual could be viewed as another component of the environment. It would thus be interesting to model the dynamics of mean fitness where the level of relatedness is coevolving with the population (Bijma et al. 2007). This will not generate new evolutionary outcomes but may shed a new light on the evolution of cooperation. Although most kin selection models rely on the simplifying assumption that population sizes are fixed, one may expect cooperation to strongly affect the demography of the population. In particular, the tragedy of the commons is a classical example of Darwinian extinction. This parable demonstrates how free access for a finite resource ultimately dooms the resource, and thus the population living upon it, through overexploitation. A way to escape overexploitation is to evolve cooperation among individuals sharing this common resource. Decoupling the effects of natural selection and the change of the environment on the dynamics of mean fitness (as we did above for another example of evolutionary suicide, see section 3.1), may help to better understand the interplay between the evolutionary dynamics of cooperation and demography.

MEAN FITNESS ACROSS ENVIRONMENTS

The study of coevolution raises many experimental challenges. Because phenotypes are often controlled by both coevolving organisms, demonstrating evolutionary change of a focal species requires measurements of the phenotypes against a reference genotype of the interacting species. For example, the evolutionary change of the virulence of myxoma virus has been demonstrated by evaluating the case mortality of virus strains sampled at different points in time, with the same reference line of rabbits (Fenner and Fantini 1999). Reciprocally, the coevolution of the rabbit population has been tracked by measuring the resistance of wild-caught individuals at different points in time against reference virus strains (Fenner and Fantini 1999). A similar approach can be used to track the changes of both host and parasite mean fitness. We illustrated the use of comparisons of mean fitness across time points in two different coevolution models. In particular, we showed that these measures may help infer some information regarding the underlying type of host-parasite specificity. The fluctuating selection and the arms race coevolutionary dynamics result in very different patterns of mean fitness across time points (Fig. 3).

Microorganisms like bacteria and viruses are particularly amenable to these approaches. First, mean fitness can be easily tracked through the measures of population growth rates. Second, the organisms from different time points can be stored in suspended animation for a very long time. For example, Buckling and Rainey (2002) realized cross infection experiments across time to detect and measure the speed of coevolution between the bacteria *Pseudomonas fluorescens* and its phage $\phi 2$. They did not measure the mean fitness (the growth rate of phage populations) but one major component of fitness: the ability of a phage population to infect bacteria populations from different time points. They found that (1) the infectivity of the phage was higher on bacteria two transfers in the past than on contemporaneous bacteria, and (2) that the infectivity of the phage was higher on contemporaneous bacteria than bacteria sampled two transfers in the future. This pattern is consistent with both models of coevolution because, in the short term, both models yield very similar dynamics (Fig. 3). Measures of phage mean fitness across more distant time points, however, may allow to distinguish between these two models. Interestingly, Decaestecker et al. (2007) conducted a similar experiment and used samples of dormant stages of *Daphnia* and their bacterial parasites archived in pond sediments to analyze, in the field, the emerging pattern of parasite adaptation across time. In contrast with Buckling and Rainey (2002) they showed that

parasites were better able to infect contemporary hosts than hosts from either past or future generations, which is consistent with the fluctuating selection dynamics of coevolution (Decaestecker et al. 2007; Gandon et al. 2008).

The above two experimental studies illustrate the relevance of the study of mean parasite fitness across time to gain some insights into the underlying evolutionary dynamics. Measures of mean fitness across space, where parasite mean fitness is evaluated in different host populations (Kawecki and Ebert 2004), have also been used to infer some information regarding the coevolutionary process, and in particular the relative rates of migration (Kaltz and Shykoff 1998; Morgan et al. 2005; Greischar and Koskella 2007). It may represent an alternative to the determination of patterns of adaptation across time when host and parasite samples from different points in time are not accessible.

Interestingly, measures of mean population fitness are relatively easy to obtain in evolutionary and coevolutionary experiments using microorganisms (e.g., bacteria and phage population growth rates). In fact, mean fitness is probably easier to measure than other phenotypic traits of microorganims (e.g., phage lysis time and burst size). We thus believe that the exploration of the dynamics of mean fitness provided in this article yields new theoretical insights on evolution and coevolution, as well as new perspectives for experimental evolution and coevolution.

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Supporting Information

The following supporting information is available for this article:

Appendix S1. Genotype frequency dynamics.

Appendix S2. Discrete time dynamics.

Appendix S3. Antigenic drift in a single epidemic.

Appendix S4. Description of the numerical simulations of Figure 2.

Supporting Information may be found in the online version of this article.
(This link will take you to the article abstract).