Beyond R_0 maximisation: on pathogen evolution and environmental dimensions

Sébastien Lion[1] and Johan A. J. Metz[2,3,4]

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[1] Centre d'Écologie Fonctionnelle et Évolutive, CNRS, Université de Montpellier, Université Paul-Valéry Montpellier 3, EPHE, IRD, 1919, route de Mende, 34293 Montpellier Cedex 5, France
[2] Evolution and Ecology Program, International Institute of Applied Systems Analysis, A-2361 Laxenburg, Austria
[3] Mathematical Institute & Institute of Biology, Leiden University, P.O. Box 9512, 2300RA Leiden, The Netherlands
[4] Netherlands Centre for Biodiversity, Naturalis, P.O. Box 9517, 2300RA Leiden, The Netherlands

Corresponding author: Lion, S. (`sebastien.lion@cefe.cnrs.fr`)

Abstract

A widespread tenet is that evolution of pathogens maximises their basic reproduction ratio, R_0. The breakdown of this principle is typically discussed as exception. We argue that a radically different stance is needed, based on ESS arguments that take account of the "dimension of the environmental feedback loop". The R_0-maximisation paradigm requires this feedback loop to be one-dimensional, which notably excludes pathogen diversification. In contrast, virtually all realistic ecological ingredients of host-pathogen interactions (density-dependent mortality, multiple infections, limited cross-immunity, multiple transmission routes, host heterogeneity, spatial structure) will lead to multi-dimensional feedbacks.

Highlights

- Contrary to established wisdom, selection in the long run rarely favours parasites that maximise their epidemiological basic reproduction ratio, R_0.

- R_0 maximisation only occurs in models with simple forms of environmental feedback.

- In realistic hostparasite interactions, ecological processes will commonly preclude R_0 maximisation.

- The dimension of the environmental feedback loop here emerges as a unifying concept.

1 R_0 maximisation and the adaptive theory of virulence

The idea of R_0 maximisation is intimately linked with the development of the adaptive theory of virulence (Anderson and May, 1982). Virulence has long been thought of as a transient state in pathogen evolution, with avirulence being the expected long-term evolutionary endpoint (Smith, 1904, Ball, 1943, Méthot, 2012), based on the rationale that harming the host would deplete the pathogen's resource. This 'classical wisdom' was challenged by modern adaptive explanations (Anderson and May, 1982, Ewald, 1983), according to which natural selection also can lead to an increase in virulence when this confers an indirect benefit to the pathogen. This happens e.g. when increasing virulence goes together with increasing transmission (the transmission-virulence trade-off hypothesis, see Alizon et al. (2009) for a review). More generally, virulence may be connected to other disease parameters, such as recovery, or within-host competitive ability. Virulence is predicted to evolve towards intermediate values whenever such connections are sufficiently strong.

The textbook explanation for evolution towards intermediate virulence assumes that long-term evolution results in maximising the following quantity,

$$R_0 = \frac{\beta S}{\mu + \alpha + \gamma}, \tag{1}$$

known as the basic reproduction ratio. In Equation (1), βS is the rate at which an infected host produces new infections in a susceptible population of density S, α the virulence, equated to pathogen-induced mortality, μ the mortality rate of uninfected hosts, and γ the recovery rate. Equation (1) has great didactic power, as it immediately shows that, even though an increase in virulence has a direct negative effect on R_0, it can also have indirect positive effects if transmission increases with virulence, or recovery decreases with virulence. The virulence that maximises R_0 thus depends on the trade-off between virulence and other disease parameters. This idea has been extremely influential and has been shaping the theory of virulence evolution ever since (Ebert and Herre, 1996, Alizon et al., 2009, Schmid-Hempel, 2011). However, the apparent simplicity of the argument obfuscates two caveats, as we discuss below. First, the basic reproduction ratio R_0 can only be written in the form (1) under strong assumptions on the epidemiological dynamics (Diekmann et al., 1990). The transmission-virulence trade-off hypothesis on the other hand fits a far larger class of epidemiological scenarios. Second, there is absolutely no guarantee that evolution selects for trait combinations maximising the R_0 of such a scenario: virtually all realistic ecological ingredients of natural host-pathogen interactions flout the R_0-maximisation paradigm.

Although the theoretical literature has repeatedly emphasised these caveats (Bremermann and Thieme, 1989, Dieckmann, 2002, Dieckmann and Metz, 2006, Thieme, 2007, Svennungsen and Kisdi, 2009, Ferdy and Gandon, 2012, Cortez, 2013), this has had less impact than deserved. The idea that pathogens evolve to maximise their basic reproduction ratio is still a cornerstone of textbook discussions of virulence evolution. This idea thus remains widespread in the community, despite regular corroboration in discussions of the experimental evidence that this is far from general (e.g. Ebert and Herre (1996)).

One possible explanation for this state of affairs is that empirical and theoretical examples where R_0 maximisation fails are typically discussed as exceptions, instead of from a general conceptual perspective. Our aim in this paper is to provide such a perspective through the notion of environmental feedback, i.e., the effect of a mutant substitution on the ecology and thereby on the fitness of subsequent mutants. For example, the rise in frequency of a more virulent strain may cause the population density to decrease; this in turn leads to lower density-dependent mortality, which feeds back positively on the mutant fitness. We argue that a precise distinction between pathogen fitness and the epidemiological basic reproduction ratio is a prerequisite for any discussion of the adaptive evolution of pathogens. We then discuss the main theoretical result that R_0 maximisation will only occur when the feedback through the environment is of a very simple kind and illustrate this point by reviewing the evolutionary consequences of several realistic features of host-pathogen interactions. Throughout, we emphasise that, although R_0 maximisation may once have been a useful paradigm and may still be a good didactical tool, a more general conceptual framework based on **ESS**[*1] arguments is needed for a

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[1]Terms highlighted with a star are defined in the glossary.

Glossary

ESS: A strategy that, if sufficiently common, creates an environment in which no alternative strategy can invade.

(Invasion) fitness: Per-capita growth rate of a rare mutant strain in the environment created by the resident population. This can be written as a function of the traits and of the environment, $\rho(Y|\hat{E})$, or as a function of the mutant and resident traits, $s(Y|X)$.

Fitness proxy: Any function of the traits and the environment that has the same sign as invasion fitness and therefore provides the same information about long-term evolution.

Fitness component: A property of the traits (and possibly the environment) that enters into the calculation of, but is not on its own sufficient to compute a fitness proxy.

Optimisation principle: A function $\psi(X)$ of the traits such that, for any constraint on the traits, the ESSes can be calculated by maximising this function (for instance, R_0 in the classical SIR model).

Pessimisation principle: A function $\phi(E)$ of the environment which is minimised at an ESS, for any constraint on the traits (for instance, the density of susceptibles in the classical SIR model).

Effective dimension of the environmental feedback loop: The term dimension of the feedback loop refers to the number of environmental variables (like the density of susceptible hosts) that are controlled by the population dynamics of the pathogen and influence $\mathcal{R}$ in different manners. However, for ESS calculations, only the sign of $\mathcal{R} - 1$ matters. The term effective dimension refers to the number of variables that independently influence this sign. In simple models, the effective dimension and the dimension are often equal but in structured models exceptions where the effective dimension is lower are commonplace.

proper understanding of the evolution of infectious diseases.

2 R_0 in epidemiological models

The general definition of R_0 in life-history theory is "the average lifetime offspring number in a given environment". In epidemiology, R_0 is typically defined as the average number of secondary infections produced by a single infected host *in an otherwise uninfected host population* (Macdonald (1952), Dietz (1975), Anderson and May (1982), Diekmann et al. (1990), Van den Driessche and Watmough (2002); see Heesterbeek and Dietz (1996) for its historic roots). The emphasis on "uninfected hosts" is crucial because R_0 is not only a function of the pathogen traits, X, but also of the environment, E, experienced by the pathogens. We may thus write $R_0(X|E)$, where in general X and E comprise more than one variable. For instance, the environment could collect the densities of susceptible and partially resistant hosts. The dependence on the environment reflects our intuition that pathogen spread will be hindered if the environment is less favourable, for instance if the frequency of resistant hosts is high.

For a pathogen to spread in an initially uninfected population, an infected individual must produce more than one secondary infection. Hence, the following condition must hold:

$$R_0(X|E_0) > 1 \tag{2}$$

where E_0 is the environment produced by the dynamics of the host population in the absence of the pathogen. In the epidemiological literature, $R_0(X|E_0)$ is generally shortened as R_0. We shall follow this convention and write $R_0(X)$ for $R_0(X|E_0)$. To distinguish this from the more general case, we

Box 1: The many guises of R_0

The general argument we give in this article also extends to more general ecological scenarios. Indeed, although R_0 has become a cornerstone of epidemiological thinking, the historical roots of the concept are in demography and life-history theory. Here, we give a brief historical perspective to shed light on these connections.

R_0 **in demography** In epidemiology, the "0" in R_0 is often interpreted as referring to the uninfected population, but the notation actually comes from human demography, where R_0 was first defined by Dublin and Lotka (1925) as the zeroth in a series of moments of the so-called reproduction kernel, i.e., the mean rate of producing kids as a function of age.

R_0 **in life-history theory** The R_0 concept was put to good use in life-history theory, where it is generally taken to be the life-time offspring production of ordinary individuals with a sequestered germ line. For general ecological scenarios, R_0 can be calculated as the dominant eigenvalue of the so-called next-generation operator that, in the given environment, projects the state of the population from one generation to the next (Diekmann et al., 1990).

R_0 **in epidemiology** The calculation of R_0 in epidemiology proceeds in the same manner as in life history theory. However, although it is a pathogen property, it is defined at a higher level, that of infected hosts. From a fundamental perspective a population of infected hosts is a metapopulation of pathogens, and the epidemiological R_0 thus corresponds with the R_0-like concepts for metapopulations, like R_m (Metz and Gyllenberg, 2001, Ajar, 2003, Massol et al., 2009) in evolutionary ecology.

On notation In the main text, we use different notations for the basic reproduction ratios computed in the pathogen-free population, $R_0(X)$, and in another environment where the host population is already infected by resident pathogen strains, $\mathcal{R}(X|E)$. This is done for clarity, but the common conceptual underpinning should be kept in mind.

use $\mathcal{R}(X|E)$ to represent the basic reproduction ratio calculated in another environment E (see also Box 1).

In practice, the calculation of $R_0(X)$ as a function of pathogen parameters will lead to different expressions depending on the life cycle of the host-pathogen interaction one considers. For instance, $R_0(X)$ does not take the same form for directly transmitted and vector-borne pathogens (Diekmann et al., 1990, Van den Driessche and Watmough, 2002). However, most discussions on pathogen evolution start with expression (1), which is obtained in the classical Susceptible-Infected-Recovered (SIR) epidemiological model (Box 2).

Let us assume that the traits of the pathogen may affect transmission (β), virulence (α), and recovery (γ), reflecting potential trade-offs between life-history traits (Anderson and May, 1982, Alizon et al., 2009). Then, in the SIR model, $R_0(X)$ can be written as

$$R_0(X) = \frac{\beta(X)}{\mu + \alpha(X) + \gamma(X)} \, S_0. \tag{3}$$

where S_0 is the equilibrium density of susceptible hosts in the absence of the pathogen (Box 2).

Equation (3) shows that, for the SIR model, the basic reproduction ratio equals the lifetime "infection pressure" by an infected individual ($\beta(X)/(\mu + \alpha(X) + \gamma(X))$), which is an individual-level property), times a single environmental variable, S_0 (the density of susceptible hosts in a pathogen-free population, which is a population-level property). This distinction between individual and population-level properties will prove essential in the next sections.

Box 2: The standard SIR model

The standard SIR model divides the host population into three compartments: susceptible (S), infected (I) and recovered (R) hosts. The model assumes that the disease is only transmitted horizontally through direct contacts with an infected host. Transitions between compartments are due to transmission and recovery events. Hosts can be removed from the population through mortality, while new susceptible hosts are created through reproduction. This is depicted in the following diagram
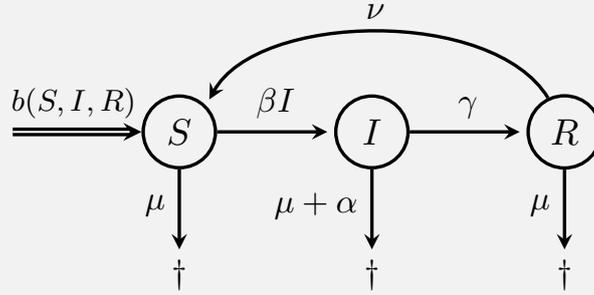
The dynamics of each class of hosts can then be captured by the following system of differential equations

$$\frac{\mathrm{d}S}{\mathrm{d}t} = b(S, I, R) - \mu S - \beta S I + \nu R \tag{a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta S I - (\mu + \alpha + \gamma)I \tag{b}$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \gamma I - (\mu + \nu)R \tag{c}$$

where $b(S, I, R)$ is the birth rate into the population, μ is the natural mortality, α represents pathogen-induced mortality (often equated to virulence in the theoretical literature), γ is the per-capita recovery rate, ν is the per-capita rate of immunity loss, and β is the transmissibility of the pathogen.

In a pathogen-free population, the demography of hosts will bring the host population to an equilibrium S_0. From equation (b), an initially rare infection will grow if

$$\beta S_0 - (\mu + \alpha + \gamma) > 0,$$

which can be rewritten as the condition $R_0 > 1$ with $R_0 = \beta S_0 / (\mu + \alpha + \gamma)$.

3   The epidemiological R_0 is not pathogen fitness

Evolution results from the competition between different strains, generally one or more resident strains and the mutants that they produce. This process is endlessly repeated as new mutants keep coming and are either expelled or become new residents. Fitness is a measure of competitive prowess. In the pathogen-free environment, there is no competition among pathogens, and therefore $R_0(X)$ cannot be expected to stand as a proxy for pathogen fitness without a multitude of other assumptions. To study long-term evolution, we should rather use **invasion fitness***, defined as the per capita growth rate of the mutant population in a resident population that has reached its epidemiological attractor (Box 3). Alternatively, we can use a **fitness proxy*** like $\mathcal{R}(Y|\hat{E}) - 1$, which has the same sign as invasion fitness. This fitness proxy also relies on a basic reproduction ratio, $\mathcal{R}(Y|\hat{E})$, but one that is measured in the environment determined by the resident pathogen strains, $\hat{E}$, instead of the pathogen-free environment, E_0.

In the simple SIR model discussed above, a mutant pathogen strain with traits Y will invade if

$$\mathcal{R}(Y|\hat{E}) = \frac{\beta(Y)}{\mu + \alpha(Y) + \gamma(Y)}\hat{S} > 1. \tag{4}$$

(Box 3). Equations (3) and (4) are misleadingly similar. The critical difference is that $\mathcal{R}$ is calculated in an environment characterised by the resident community of pathogen strains, $\hat{E}$, instead of the pathogen-free environment E_0. A crucial property of this specific model is, moreover, that the effect of the environment is captured by a single variable coming in multiplicatively, the equilibrium density of susceptible hosts, $\hat{S}$. Unfortunately this property, on which the R_0 maximisation paradigm hinges, is far from general.

4   Evolution will maximise R_0 only in very simple environments

The natural stops of evolution through repeated mutant substitutions are ESSes, that is, trait combinations making it impossible for alternative feasible combinations to invade. By definition, an ESS corresponds to a maximum of pathogen fitness in the corresponding environment. This implication extends to any fitness proxy like $\mathcal{R}(Y|\hat{E})$ when $\hat{E}$ is chosen to be the environment generated by the ESS. However, the statement "evolution maximises R_0" is generally taken to mean that one can calculate the evolutionary endpoint by maximising $R_0(X)$, which is simply a function of X, the environment being fixed at its disease-free value E_0. It is thus taken for granted that the environment experienced by the mutant pathogen does not matter, and that there exists a single type of pathogen that has maximal lifetime production of new infections per infected host in all possible environments. The examples in Section 5 show that we cannot in general expect the same pathogen type to perform best in both disease-free and already infected populations.

A necessary and sufficient condition for evolution to maximise R_0

To elucidate under which conditions the outcome of pathogen evolution can be determined by maximising the epidemiological R_0, it is helpful to turn to more general results on the conditions for the existence of an **optimisation principle***. The latter simply means a function of the traits, $\psi(X)$, such that that we can find potential ESSs by maximising this function. The question "when does evolution maximises R_0?" then becomes "when is $R_0(X)$ an optimisation principle"? It turns out that this occurs if and only if the pathogen fitness can be written as

$$\mathcal{R}(Y|\hat{E}) = \left[R_0(Y)\phi(\hat{E})\right]^{q(Y,X)} \tag{5}$$

with q a positive function of the traits (Metz and Geritz, 2016). That is, the effect of the environment can be summarised by a function $\phi(\hat{E})$ that multiplicatively affects the epidemiological basic reproduction ratio $R_0(Y)$. For instance, in the SIR model, we can simply obtain the fitness proxy $\mathcal{R}$ (equation 4) by multiplying R_0 (equation 3) with a function of the environment $\phi(\hat{E}) = \hat{S}/S_0$, so that condition (5) is satisfied with $q(Y, X) = 1$.

Box 3: How should we define pathogen fitness?

To make prediction about long-term evolution, the adaptive dynamics (Geritz et al., 1998, Metz, 2012) framework provides us with a standardised procedure to calculate the fitness of pathogens. If the mutation rate is low, we may assume a separation of time scales between epidemiological and evolutionary dynamics. In other words, we may assume that the environment reaches an epidemiological attractor $\hat{E}(X)$ before a new mutation with trait value, say, Y occurs. With this assumption, the relevant measure of pathogen fitness is the invasion fitness, $\rho(Y|\hat{E})$, which measures the growth of the mutant population in a resident population that has reached its epidemiological attractor. Alternatively, we can use any fitness proxy that has the same sign as $\rho(Y|\hat{E})$. For instance, we can measure population increase in generation time and use $\ln \mathcal{R}(Y|\hat{E})$ or $\mathcal{R}(Y|\hat{E}) - 1$ as a fitness proxy.

Pathogen fitness in the SIR model To fix ideas, let us return to the simple SIR model discussed above. The epidemiological attractor is an endemic equilibrium $(\hat{S}, \hat{I}, \hat{R})$. From the dynamics of the density of hosts infected by the mutant parasite, we have, if we make the usual assumption that recovery from any strain confers immunity to all,

$$\rho(Y, \hat{E}) = \beta(Y)\hat{S} - (\mu + \alpha(Y) + \gamma(Y)).$$

The mutant strain invades if $\rho(Y, \hat{E}) > 0$. Alternatively, this condition can be rewritten as $\mathcal{R}(Y|\hat{E}) > 1$, where

$$\mathcal{R}(Y|\hat{E}) = \frac{\beta(Y)}{\mu + \alpha(Y) + \gamma(Y)}\hat{S}. \tag{a}$$

Although in the SIR model, there is no real practical benefit in using $\mathcal{R}$ instead of ρ, fitness proxies can often considerably simplify the calculations in more complicated ecological scenarios. (A further fitness proxy that in complicated situations is algebraically far simpler, but less interpretable, than R_0 can be found in Metz and Leimar (2011).)

One thousand and one expressions for pathogen fitness Equation (a) is only one of the many expressions for pathogen fitness derived in the theoretical literature when the simplistic assumptions underpinning the SIR model are relaxed. For instance, minor extensions of the SIR model often lead to expressions of the form

$$\mathcal{R}(Y|\hat{E}) = \frac{\beta(Y)\hat{S} + \tau(\hat{E})}{\mu + \alpha(Y) + \gamma(Y) + \delta(\hat{E})}, \tag{b}$$

where the environmental feedback affects both pathogen transmission (through the term $\tau(\hat{E})$) and the average lifetime of hosts infected by the mutant pathogen (through the term $\delta(\hat{E})$). Examples include models with density-dependent mortality (equation (7)), superinfection (equation (8)), limited cross-immunity (equation (9)) or vertical transmission (equation (10)).

If condition (5) holds, the full ESS calculation is mathematically equivalent to maximising $R_0(X)$ (Mylius and Diekmann, 1995, Metz et al., 2008). To see this, note that at the resident equilibrium, we have $\mathcal{R}(X|\hat{E}) = 1$, which implies $\phi(\hat{E}) = 1/R_0(X)$. Thus, $\mathcal{R}(Y|\hat{E})$ is greater than 1 if and only if $R_0(Y) > R_0(X)$, which leads to the maximisation of R_0. In Section 5, we shall see that condition (5) can be used to quickly judge whether a given epidemiological model supports an optimisation principle or not.

Consequence 1: The evolutionary maximisation of R_0 is equivalent to the minimisation of the susceptible density

The grand idea of R_0 maximisation has a more downbeat counterpart. Instead of looking at whether evolution maximises a function of the trait, $\psi(X)$, one may look at the impact of trait evolution on the environment, $\phi(\hat{E})$. For our baseline SIR model, we have $\phi(\hat{E}) = \hat{S}/S_0 = 1/R_0(X)$. Hence, maximising $R_0(X)$ is equivalent to minimising the equilibrium density of susceptible hosts

$$\hat{S} = \frac{\mu + \alpha(X) + \gamma(X)}{\beta(X)}. \tag{6}$$

Any mutant that is favoured by evolution has a higher $R_0(X)$, but makes for a lower density of its resource. The process ends when the density of susceptible hosts is so low that no other mutant pathogen can invade. From the pathogen's view evolution thus leads to the worst attainable world, a result dubbed **pessimisation principle*** (Mylius and Diekmann, 1995, Metz et al., 2008). Pessimisation principles occur in all models with an optimisation principle. In a purely ecological context, they appear as the principle that among species competing for a single resource only the type survives that tolerates the lowest resource density. Similarly, SIR-type epidemiological models tell that a community of parasites will ultimately be dominated by the strain with the highest R_0 (Anderson and May, 1982), which also results in the lowest susceptible density that allows the disease to persist.

The dimension of the environmental feedback loop

A crucial feature of equation (5) is that the effect of the environment can be summed up by a single number, $\phi(\hat{E})$, such that increasing ϕ can only change the sign of $\mathcal{R} - 1$ from negative to positive (Metz et al., 2008). An environmental feedback of this form is said to be effectively one-dimensional, because only one variable is needed to describe the effect of the environment on the fitness sign. For instance, in the SIR model, increasing the density of susceptible hosts can only cause $\mathcal{R}$ to go from below 1 to above 1. In such simple environments, selection maximises a model-dependent function of the traits, $\psi(X)$, which only in the simplest scenarios will be $R_0(X)$ (Metz et al., 2008).

Conversely, any model for which the environmental feedback cannot be effectively summed up by only one variable does not allow for the ESS to be calculated through maximising R_0 (Metz et al., 2008). Which is the case can be decided by checking whether the pathogen fitness $\mathcal{R}(Y|\hat{E})$ satisfies condition (5). In Section 5, we review a diversity of biological mechanisms that generically give rise to multi-dimensional environmental feedback loops and thereby cause R_0 maximisation to break down. The long-term evolutionary outcome then can only be found from a full ESS calculation.

Consequence 2: R_0 maximisation excludes diversification

If an optimisation principle exists (in particular if evolution maximises R_0), the evolutionary process is of the simplest kind: any mutant that increases the optimisation criterion goes to fixation, until an ESS is reached, so that any ESS is an evolutionary attractor and vice versa (Metz et al., 2008). This has one important corollary: polymorphisms are impossible. Thus, a prerequisite for the evolutionary diversification of pathogen populations is that evolution does not maximise anything, and does not maximise R_0 in particular. The R_0 maximisation paradigm thus faces an immediate empirical challenge, because it is incompatible with any longer term coexistence of different pathogen strategies in nature.

Consequence 3: ESS trait values often differ from those obtained from R_0 maximisation

When the environmental feedback loop is not conducive to diversification, using R_0 maximisation to predict the endpoint of evolution usually leads to quantitative errors. In principle, the magnitude of such errors can be inferred from the structure of the model. Figure 1 shows a graphical tool for deducing what kind of influence the environmental feedback loop may exert. We start by noting that, under a trade-off between transmission and virulence, R_0 maximisation can be cast in a form corresponding to the so-called Marginal Value Theorem (Charnov, 1976), which allows the ESS to be found graphically, as depicted in Figure 1a. Suppose for instance that the effect of the environmental feedback loop affects the average time a mutant pathogen hangs on to an infected host (an effect captured in equation (b) in Box 3 by the term $\delta(\hat{E})$). This would happen for instance when a more virulent resident strain causes a decline in population density, which in turn decreases the density-dependent mortality rate experienced by a mutant parasite. In this case, the graphics tells that this feedback increases or decreases the ESS relative to the outcome of R_0 maximisation depending on whether in the example under consideration the added term is positive or negative (Figure 1b,c). The size of the error made by using R_0 maximisation instead of the full ESS calculation depends on the curvature of the trade-off (Appendix S8). If the value of virulence α_O^* that maximises R_0 lies on a fairly straight section of the trade-off, as in Figure 1b, any small shift from O to A will cause a large deviation of the ESS compared to α_O^*. In contrast, in Figure 1d, where the trade-off has a high curvature around α_O^*, the same shift from O to A will have negligible effect.

5 Most biological scenarios jar with the R_0 maximisation paradigm

The preceding discussion gives a general argument for why the principle of R_0 maximisation can be expected to be misleading, either qualitatively or quantitatively, for the majority of epidemiological scenarios. We will now illustrate this general argument for a selection of more realistic biological scenarios. Using the SIR model as baseline, we highlight salient biological factors causing ESS predictions to deviate from the purported predictions coming from an R_0 maximisation (see e.g. Ebert and Herre (1996), Schmid-Hempel (2011) for reviews in the non-theoretical literature). The aim of our non-exhaustive review is to emphasise the unifying principle connecting these different scenarios, which is to be found in the dimension of the environmental feedback loop. To keep things simple, we use the classical assumption of a trade-off between transmission and virulence (see Alizon et al. (2009) for a review) and focus on populations at endemic equilibrium (but see Appendix S7 for a discussion of non-equilibrium epidemiological attractors).

5.1 Density-dependent mortality

The classical SIR model assumes that density-dependence only affects fecundity. However, density-dependent mortality has for example been identified as a key factor of the evolutionary dynamics of Marek's disease in poultry farms (Rozins and Day, 2017). To take this into account, suppose now that μ is a function of the host densities, say $\mu = \mu_0 + \kappa N$, where $N = S + I + R$ is the total host density. Indicating the mutant properties with a prime, so that e.g. $\mathcal{R}' = \mathcal{R}(\alpha', \beta'|S, I, R)$, we obtain the following fitness proxy

$$\mathcal{R}' = \frac{\beta' \hat{S}}{\mu_0 + \kappa \hat{N} + \alpha' + \gamma}. \tag{7}$$

With this simple increment in ecological realism, the environmental feedback affects pathogen fitness in two contrasting ways: as before, pathogen transmission is proportional to the density of susceptible hosts, $\hat{S}$, but, in addition, the duration of infection also decreases with the total population density of the residents, $\hat{N}$, allowing the residents trait to exert an additional influence on the fitnesses of mutants. Thus, unless very stringent assumptions are made, the effective dimension of the feedback loop is two, i.e., there is no way we can sum up the effect of the environment by a single number as in condition (5). As a result, evolution does not maximise any purported environment-independent fitness proxy. This may notably lead to evolutionary branching (Andreasen and Pugliese, 1995, Dieckmann
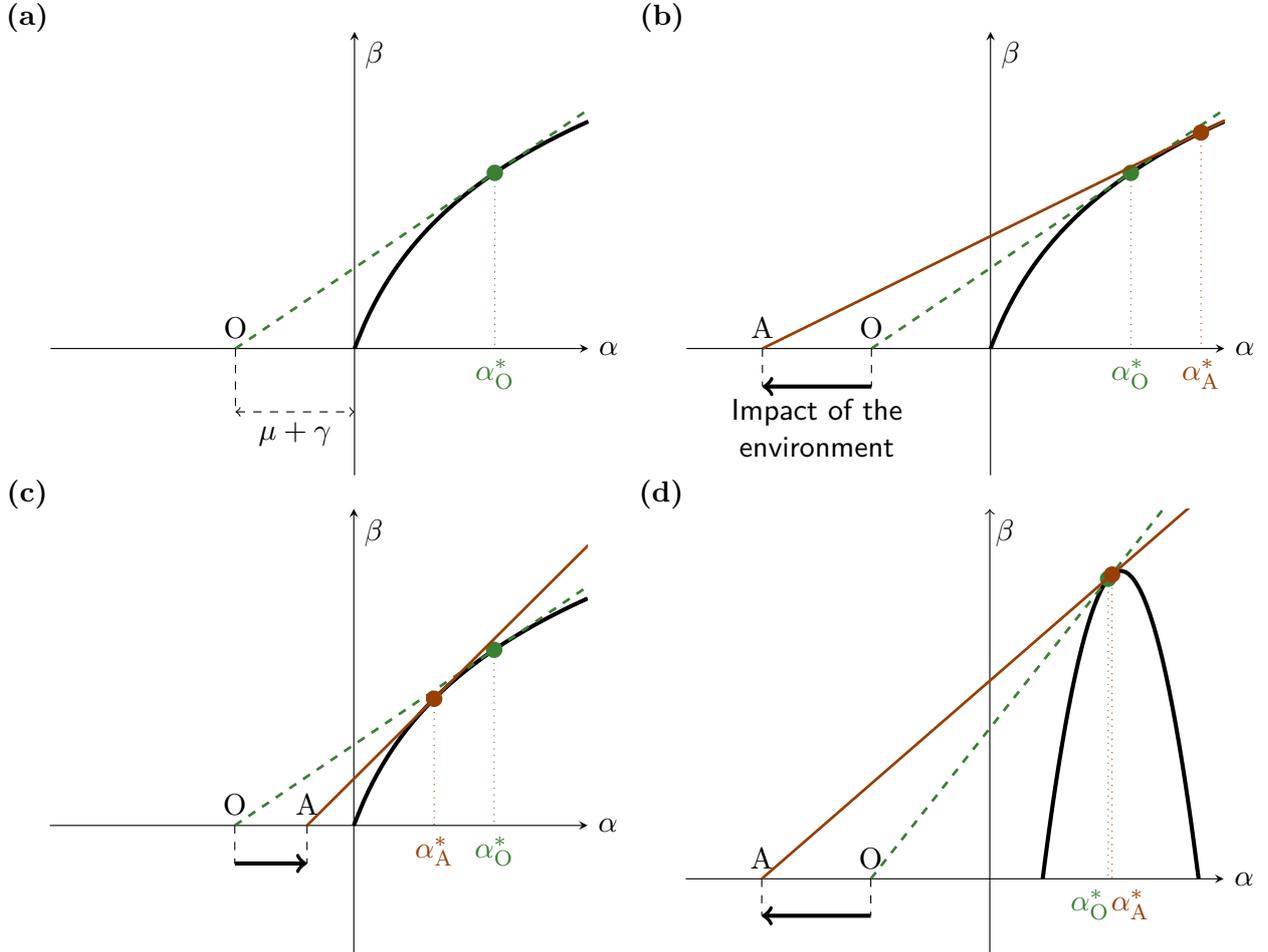
Figure 1: **A graphical derivation of quantitative consequences of R_0 (non-)maximisation.** – (a) Assuming a simple trade-off between transmission (β) and virulence (α), R_0 maximisation in the SIR model implies that the ESS (α_O^*) can be found graphically by drawing the tangent at the trade-off curve that goes trough the point O $= (-\mu - \gamma, 0)$. (b) With slightly different expressions for pathogen fitness, for instance as given by equation (b) in Box 3, the ESS α_A^* will deviate from the prediction of R_0 maximisation due to the additional effect of the environmental feedback loop captured by the term $\delta(\hat{E})$. The tangent at the ESS then goes through the point A $= (-\mu - \gamma - \delta(\hat{E}), 0)$. If $\delta(\hat{E})$ is positive, the point A is to the left of point O and selection favours higher virulence than predicted by R_0 maximisation. (c) In contrast, a negative value of $\delta(\hat{E})$ leads to lower virulence at ESS. (d) The size of the discrepancy $\alpha_A^* - \alpha_O^*$ is inversely proportional to the curvature of the trade-off around the value of virulence α_O^* that maximises R_0 (compare with panel (b)).

and Metz, 2006, Svennungsen and Kisdi, 2009), but even when long-term evolution converges to a monomorphic ESS (Dieckmann, 2002, Pugliese, 2002), the ESS will deviate from the value predicted by R_0 maximisation. Figure 1c graphically depicts this deviation. In this model, the effect of the environment is $\kappa(\hat{N} - S_0)$ (Appendix S1). If, as expected, the presence of the pathogens leads to a decrease in the total population size, $\hat{N}$, compared to the density of hosts in an uninfected population, S_0, the point A will be to the right of O and the evolutionarily stable (ES) virulence will be lower than the value that maximises R_0.

5.2   Multiple infections

In nature, hosts are typically infected by several pathogen strains or species (Petney and Andrews, 1998, Balmer and Tanner, 2011). When different pathogen strains compete for within-host resources, higher levels of virulence can be selected for (van Baalen and Sabelis, 1995, Frank, 1996, Gandon et al., 2001a), a prediction backed up by some experimental results in malaria (de Roode et al., 2005). As an illustration, assume that hosts infected by strain i, if additionally infected by strain j, are then taken over with probability σ_{ji} following rapid within-host competition (so-called superinfection May and Nowak (1994)). For a monomorphic resident population, we only need to consider the resident (r) and mutant (m) strains. We then have the following fitness proxy (Appendix S2; Gandon et al. (2001a))

$$\mathcal{R}' = \frac{\beta'(\hat{S} + \sigma_{mr}\hat{I})}{\mu + \alpha' + \gamma + \sigma_{rm}\beta\hat{I}}. \tag{8}$$

The feedback of the environment acts through the densities of both susceptible and infected hosts. The total density of hosts that can be infected by a mutant pathogen, $\hat{S} + \sigma_{mr}\hat{I}$, acts as a first feedback variable, with a positive effect on the transmission of all mutant pathogens, the more so for mutants that are better at taking over a resident-infected host (high σ_{mr}). However, a high density of resident-infected hosts, $\hat{I}$, will also increase the risk of a resident take-over (through the term $\sigma_{rm}\beta\hat{I}$) for mutant-infected hosts, resulting in a reduced infection duration, the more so the better the resident is at such a take-over (high σ_{rm}). The presence of two independent feedback variables implies that the long-term evolutionary outcome cannot be predicted by a simple R_0 maximisation. Many theoretical studies have investigated the evolutionary consequences, with three main conclusions: First, superinfection models readily produce evolutionary branching leading to the coexistence of strains with different host exploitation strategies (Boldin and Diekmann, 2008, Boldin et al., 2009, May and Nowak, 1994, Adler and Mosquera Losada, 2002). Second, even when diversification is impossible, the ES virulence will be typically higher than the value that maximises R_0, as captured by figure 1b (point A is to the left of O). Third, the precise evolutionary outcome will generally be due to both the direct effect of within-host competitiveness and the indirect effect of the environmental feedback loop that comes from the take-over pressure by resident pathogens on mutant-infected hosts (see Appendix S2 for details).

5.3   Limited cross-immunity

The classical SIR model assumes full cross-immunity, so that recovered hosts are equally immune to all pathogen strains. However, if mutant pathogens can also infect hosts that have recovered from the resident infection, we obtain the following fitness proxy:

$$\mathcal{R}' = \frac{\beta'}{\mu + \alpha' + \gamma}(\hat{S} + (1 - c(\alpha', \alpha))\hat{R}) \tag{9}$$

where $c(\alpha', \alpha)$ measures cross-immunity. Full cross-immunity implies $c = 1$, in which case equation (9) satisfies condition (5). A reasonable assumption is that cross-immunity is less for more dissimilar trait values. A detailed analysis (Appendix S3) then shows that the evolutionary dynamics will converge towards the value of virulence that maximises R_0, as in the SIR model with full cross-immunity. However, because c acts similar to a trait-dependent competition coefficient, this value can be a branching point at which the evolutionary path starts to diversify, leading to the coexistence of virulent and prudent pathogens. Several models incorporating limited cross-immunity have indeed demonstrated such diversification (e.g. Adams and Sasaki (2007), Alizon and van Baalen (2008), Best

and Hoyle (2013)). Hence, although the initial evolutionary dynamics may give the impression that R_0 is maximised, this is not predictive of long-term evolution.

5.4   Multiple transmission routes

So far, we have only considered pathogens with direct horizontal transmission. Multiple transmission routes are another ubiquitous factor causing an increase in the dimension of the environmental feedback loop. In pathogens with both horizontal and vertical transmission, selection has been found to favour pathogens with suboptimal values of R_0 (Nowak, 1991, Lipsitch et al., 1996, Messenger et al., 1999, Ferdy and Godelle, 2005, Cortez, 2013). To understand why, extend the SIR model by allowing the pathogen to be transmitted vertically with probability ϵ. If $b'_{\mathrm{I}}(N)$ denotes the density-dependent fecundity of hosts infected by the mutant strain, where N is the total population size, this leads to

$$\mathcal{R}' = \frac{\beta' \hat{S} + \epsilon b'_{\mathrm{I}}(\hat{N})}{\mu + \alpha' + \gamma} \tag{10}$$

(see Appendix S4 for details). Vertical transmission thus introduces a dependence of fitness on the total population density, in addition to the density of susceptible hosts, and we now have two independent feedback variables. Therefore, according to our general criterion, looking for an optimisation criterion is bound to fail. The key point is not the distinction between horizontal and vertical transmission but the different forms of density dependence introduced by each transmission route. In general, multiple transmission pathways (e.g. sexual vs. non-sexual transmission Thrall and Antonovics (1997), direct vs. environmental transmission Day (2002), Boldin and Kisdi (2012)) introduce separate environmental feedback variables. This may lead to diversification of the pathogen population (Thrall and Antonovics, 1997, Boldin and Kisdi, 2012, Bernhauerová and Berec, 2015, Hamelin et al., 2016). When there is no diversification, arguments similar to those of Figure 1 show that the ESS value of α is smaller than that coming from R_0 maximisation, with the size of the error again inversely proportional to the trade-off curvature (Appendix S4).

5.5   Host heterogeneity

Most host populations exhibit among-host variation in quality or immune status. This heterogeneity can reflect genetic variation in host resistance or tolerance (Dwyer et al., 1997, Råberg et al., 2007, Keith and Mitchell-Olds, 2013), sex-based dimorphism (Nunn et al., 2009), nutritional status, infection history, senescence, environmental factors (Sorci et al., 2013b,a), different coinfections (van Baalen and Sabelis, 1995, Gandon, 2004, Lion, 2013), or just different host species. Because the reproductive potential of the pathogen is likely to differ between host classes, host heterogeneity will generally affect pathogen evolution (Gandon, 2004), as shown in host populations with sexual dimorphism (Cousineau and Alizon, 2014, Úbeda and Jansen, 2016) or intermediate vaccination coverage (Gandon et al., 2001b, 2003). Because each class of host potentially produces a separate environmental feedback variable, evolution will optimise some function of the traits only under very specific assumptions on the patterns of infection across classes (see Box 4). In principle, host heterogeneity can favour evolutionary branching, because each host class may act as a potential niche for the pathogen. This effect is particularly strong when hosts and pathogens coevolve, in which case diversification in one species can readily lead to the co-diversification of the other species (Pugliese, 2011, Best et al., 2009, 2010).

5.6   Spatial structure

In nature, patterns of local host and pathogen dispersal lead to the build-up of genetic and epidemiological structure, with deep implications for the evolutionary ecology of host-pathogen interactions (Greischar and Koskella, 2007, Jousimo et al., 2014, Tack and Laine, 2014, Lion and Gandon, 2015, Parratt et al., 2016). Consider for instance that infectivity decreases with distance. Then, the effective density of susceptible hosts that can be infected by a focal host infected by a mutant pathogen,

Box 4: Some evolutionary consequences of host heterogeneity

Pathogen evolution in heterogeneous host populations strongly depend on the pattern of infection across host classes. For a pathogen that can infect two classes of hosts (A and B), different cases can be distinguished.

Unbiased transmission   Denoting τ_{ij} the transmission rate from class i to class j, this occurs if $\tau_{AA}\tau_{BB} = \tau_{AB}\tau_{BA}$. This property is satisfied in many models that assume that transmission is the product of infectivity and susceptibility, i.e. $\tau_{ij} = \beta_i\sigma_j$, where σ_j is the susceptibility of host class j. Biologically, this means that pathogen propagules all pass through a common pool (cf Rueffler and Metz (2013)). Then, pathogen fitness can be written as the sum of the basic reproduction ratios in each class of hosts (Gandon et al., 2001b, Gandon, 2004)

$$\mathcal{R}' = \frac{\beta'_A}{\mu + \alpha'_A + \gamma'_A}\sigma_A\hat{S}_A + \frac{\beta'_B}{\mu + \alpha'_B + \gamma'_B}\sigma_B\hat{S}_B.$$

The fitness proxy depends on two environmental variables, which are the equilibrium densities of susceptible hosts in each class, $\hat{S}_A$ and $\hat{S}_B$. These are given by

$$\hat{S}_A = \frac{\mu + \alpha_A + \gamma_A}{\sigma_A h/\hat{I}_A} \qquad \text{and} \qquad \hat{S}_B = \frac{\mu + \alpha_B + \gamma_B}{\sigma_B h/\hat{I}_B}.$$

where $h = \beta_A\hat{I}_A + \beta_B\hat{I}_B$ is the force of infection. We may then distinguish two cases.

- If the two host classes only differ by their susceptibility to the disease, then pathogen fitness simplifies to the lifetime infectivity times the total density of susceptibles, $\sigma_A\hat{S}_A + \sigma_B\hat{S}_B$ (Gandon et al., 2001a). If the susceptibilities are independent of the evolving traits, condition (5) holds true. The ESS is thus unaffected by host heterogeneity and is predicted from simple R_0 maximisation using the unstructured SIR model.

- If virulence is different in the two classes, the ESS is intermediate between the optimal virulences predicted from R_0 maximisation in each class in isolation (Gandon et al., 2001b, 2003). However, there may still exist an optimisation principle if both $\hat{S}_A$ and $\hat{S}_B$ are decreasing functions of a single environmental variable, such as the force of infection h (Svennungsen and Kisdi, 2009).

Biased transmission   The above analysis breaks down if $\tau_{AA}\tau_{BB} \neq \tau_{AB}\tau_{BA}$. Then, pathogen fitness cannot be written as the sum of the contributions of each class (Gandon, 2004). This generically results in two-dimensional feedback loops, in which case there is no hope of finding a fitness proxy that is maximised by evolution.

Vector-borne diseases   A special case where R_0 maximisation can nevertheless do the job is when the two host classes are two host species that need to be exploited in strict alternation, so that $\tau_{AA} = \tau_{BB} = 0$. Then, we have

$$\mathcal{R}' = R'_0(Y)\sqrt{\frac{\hat{S}_A\hat{S}_B}{S_{0,A}S_{0,B}}}$$

where $R'_0(Y)$ is the basic reproduction ratio for a mutant vector-borne pathogen in the two-host population in the absence of the disease (see Appendix S5 for details). Hence, condition (5) holds true, and R_0 maximisation works, although the expression for R_0 is not the same as in the SIR model with direct transmission (Van den Driessche and Watmough, 2002, Cortez, 2013). However, the existence of an additional transmission route will cause deviations from the predictions of R_0 maximisation. For instance, several vector-transmitted pathogens have also been shown to be transmitted vertically (Ebert, 2013), either in the vertebrate host (e.g. *Plasmodium falciparum*) or in the vector (e.g. several arboviruses, Lequime et al. (2016)).

$[S|I']$, will be lower than the overall density of susceptible hosts in the population, S. This yields the following fitness proxy:

$$\mathcal{R}' = \frac{\beta'[S|I']}{\mu + \alpha' + \gamma}. \tag{11}$$

Although superficially similar to the non-spatial expression, equation (11) hides a further complication. Because transmission is mostly local, a mutant pathogen with a higher lifetime infection pressure will on average experience a lower density of susceptibles around it. $[S|I']$ thus depends on how the mutant's traits influence the local epidemiological structure experienced by the carriers of the mutant pathogen. As a consequence the environmental feedback loop generally can only be fully characterised by a large number of variables. However, not all is lost. If we further assume that the resident population is at equilibrium, the invasion condition can be written as

$$\left(\frac{1}{R_0^{\mathrm{NS}}} - \frac{1}{R_0'^{\mathrm{NS}}}\right) + \left([S|I'] - [S|I]\right) > 0 \tag{12}$$

where R_0^{NS} (resp. $R_0'^{\mathrm{NS}}$) denotes the lifetime infection pressure exerted by resident (resp. mutant) pathogens in the corresponding non-spatial model (Lion and Gandon, 2015). The first term between brackets on its own would lead to the maximisation of the lifetime infection pressure predicted by the non-spatial model. The second term occurs since different pathogen strains experience different densities of susceptible hosts. Therefore spatial structure is expected to affect the evolutionary outcome (Boots and Sasaki, 1999, Lion and Boots, 2010, Lion and Gandon, 2015). Further developments of inequality (12) indicate that the deviation from R_0 maximisation is determined by the balance between genetic structure (local relatedness between pathogens infecting different hosts) and a measure of epidemiological structure for evolutionarily neutral mutants (Lion and Boots (2010), Lion and Gandon (2015); see Appendix S6 for details).

6 Lessons for the future

The R_0 maximisation principle is one of many examples in science where a specific result derived for a simple model, or under a particular simplifying assumption, has been promoted to canon status. In epidemiology, other examples include the transmission-virulence trade-off and the representation of virulence as disease-induced mortality, assumptions that underpin many theoretical models. One of our messages is that irreverence for tradition is a key element of scientific progress: we should not let habits or history stifle the development of new ideas. Further progress in the study of pathogen evolution requires explicitly accounting for environmental feedbacks. In this section, we discuss the implications for empirical studies and potential applications.

6.1 Should we attempt to measure pathogen fitness?

The conclusion that selection will only rarely maximise a "measure of absolute fitness" such as $R_0(X)$ is not only of interest to theoretical biologists. Many empirical studies rely on the presumed measurement of some fitness proxy expected to be maximised by selection. This activity is seldomly informative. First, as we have seen, evolution only rarely satisfies an optimisation principle. Second, empirical measurements of fitness proxys are generally hard to come by. This is even the case for R_0 and $\mathcal{R}$ since we have to take account of the demography of the full life cycle, which often includes parts that are hard to observe. Third, even if we know how to measure a valid fitness proxy, it is rarely possible to do more than measuring it in the current environment. Then, if the population mean does not sit close to the proxy's maximum, either something went wrong or we stumbled on a case of fast ongoing evolution, and the result will probably not get reported. If the population mean does sit close to the proxy's maximum, this tells only that the population has roughly equilibrated to an ESS, but gives little information on the processes that have brought the population to this point, or where evolution will take the population after an imposed environmental change.

One could object that there is some experimental evidence of R_0 maximisation. However, only a relatively small number of experimental studies appear to support this paradigm. The myxomatosis

epidemic in Australian rabbits has been used as such an example (Anderson and May, 1982, Fenner and Fantini, 1999, Mackinnon et al., 2008). It is true that, initially, the population quickly settled to a virulence level that was relatively close to the value maximising the classical expression of R_0 (Massad, 1987, Mackinnon et al., 2008). However, the subsequent rise of resistance in Australian rabbits then selected for increased virulence (Fenner and Fantini, 1999). These two phases of the epidemic are characterised by two different environmental feedbacks: in the early years, selection was mostly driven by a strongly curved transmission-virulence trade-off (Massad, 1987), while in the later years, host heterogeneity led to a two-dimensional feedback loop which precludes R_0 maximisation (Appendix S9; see also Dieckmann (2002)). The apparent maximisation of R_0 is thus only a transient state in the coevolution of the myxoma virus and its host. In a similar vein, Fraser et al. (2007) have shown the average set-point viral load of HIV in two human cohorts to be close to the value that maximises R_0, calculated through an extension of formula (1) to age-structured populations. However, because the data from which the authors estimated the basic reproductive ratio incorporated the effect of environmental feedbacks, the authors probably estimated the fitness proxy $\mathcal{R}$ rather than the epidemiological R_0. An alternative interpretation of this result is thus that its fast evolution causes the HIV population to track a moving optimum of $\mathcal{R}(Y|E(t))$, with $E(t)$ the current environment (Appendix S10). To predict the outcome of interventions, what really matters is how a large treatment roll-out would impact the environmental feedback on HIV dynamics. This can only be achieved by combining careful empirical studies, as in Fraser et al. (2007), with the insights of more general ecological theory.

Rather than empirical support for the R_0-maximisation principle, we see these studies as an opportunity to infer conclusions about the form of the environmental feedback in these systems. In some cases, such studies may also help to identify approximate optimisation principles, which can be empirically useful when they exist. An interesting challenge for future theoretical research would be providing empiricists with a theoretical overview of the systems for which simple optimisation principles can be used, together with keys for their empirical identification (see Box Outstanding Questions). In general, however, trying to measure fitness will not necessarily be the best way to study the adaptive evolution of pathogens. Not only is it a difficult task, the eventual benefit to our understanding may often be disappointing. An alternative approach is to use simple models and ESS considerations to generate, and subsequently test, predictions phrased in terms of readily observable quantities such as the average value of a trait or the frequency of an allele. In this perspective, fitness is best viewed as a theoretical device which can be used to make predictions on more directly measurable properties of biological systems.

6.2 Applications and generalisations

Although for the sake of simplicity we focussed on the evolution of virulence, there is more to host-pathogen evolution than just virulence. Our main message applies generally to life-history traits affecting the dynamics of host-pathogen interactions, and thus pertains equally to other problems such as the evolution of drug resistance or vaccine escape. All this has obvious practical implications for the short- and long-term management of infectious diseases, where one is interested in the evolutionary consequences of some external interference, such as treatments or control measures. For long-term predictions, we have to think beyond adaptations to observed circumstances and consider evolutionary changes of trait values in concert with the environmental changes induced by them. As we have shown, the principle of R_0 maximisation is then of limited use, and we need a more predictive theory, for which we gave some conceptual foundations. At the other extreme, it has long been known that, for short-term predictions, R_0 maximisation is misleading, because strains with higher per-capita growth rates but lower R_0 can be favoured transiently (Lenski and May, 1994, Frank, 1996, Day and Gandon, 2007, Bull and Ebert, 2008). Hence, if we want to make predictions about the immediate consequences of a therapeutic intervention, we need to think carefully about how environmental feedbacks play out during transient epidemiological dynamics (see Box Outstanding Questions).

The message of this article is also relevant for more general problems in evolutionary biology. In fact, the line of argument that we followed here was developed for the evolution of life-history traits in general ecological systems (Metz et al., 2008). The many pressing challenges facing today's

Box 5: Outstanding Questions

- **How can we identify biological systems supporting approximate optimisation principles?** For some systems, approximate optimisation principles may be sufcient to predict long-term evolution. Finding guidelines for identifying such systems could prove useful for empirical and experimental studies.

- **Can we construct useful fitness proxies from simple considerations of the life-cycle of hostparasite interactions?** Finding good measures of fitness is a challenge for many empiricists. While the epidemiological R_0 cannot in general be expected to be a valid fitness proxy, a key motivation for further theoretical research is to provide disease ecologists with recipes to build fitness proxies from simple biological observations.

- **How important are host and parasite population structures in shaping selection on parasite traits?** Given that population structure (such as age or spatial structure) can be expected to lead to higher-dimensional environmental feedbacks, we need to better understand to what extent and in which manner such structures influence the outcomes of evolution.

- **How do environmental feedbacks shape pathogen evolution during transient dynamics?** We have assumed here that evolution is slow compared with ecology but, for many host-pathogen systems, evolution may be faster, or unfold on similar timescales. Disease management calls for theory of pathogen evolution during transient epidemiological dynamics.

evolutionary biologists are all characterised by multi-dimensional feedbacks between ecological and evolutionary dynamics. To understand the consequences of climate change, habitat fragmentation, or the harvesting of natural resources, an approach based on optimisation does not suffice.

7   Concluding remarks

What should a first-principles-based view on the rationale of evolutionary epidemiology look like? For long-term predictions, we see ESS theory and its dynamic counterpart adaptive dynamics, both anchored in the concepts of invasion fitness and dynamical fitness landscapes, as its main pillars. R_0 optimisation did a great job in the early days, but should no longer keep its primacy in teaching and presumed applications since it only finds ESSes under very restrictive conditions. Emphasising it therefore puts new generations of researchers in the wrong starting block. The challenges raised by emergent infectious diseases, to name but one of the many modern predicaments, require that we give our students the best possible conceptual starting point for tackling the world, and R_0 optimisation fails to fit that bill. The time is ripe for more accurate (and exciting!) approaches to pathogen evolution.

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Supplementary Online Material

In this appendix, we present a more detailed analysis of the various special cases discussed in the main text. Of course, a full study is beyond the scope of this paper (and besides, the literature already provides much better and complete analyses). Our more modest aim is to collect here some technical justifications that we could not give in the main text without disrupting the flow of the argument.

S.0 Calculating ESSes

We recall here the recipe for calculating ESSes; it derives from the idea that an ESS sits at the top of its self-created fitness landscape: Maximise $\mathcal{R}(Y|\hat{E}(X))$ over Y to end up with a function Y_{opt} of X, and then solve $Y_{\text{opt}}(X^*) = X^*$. The maximisation can be done numerically or sometimes analytically by setting the derivative of $\mathcal{R}(Y|\hat{E}(X))$ for Y equal to zero. In the latter case the equation $Y_{\text{opt}}(X^*) = X^*$ may be solved again either analytically or numerically. In the first case all equations have to be solved numerically. This is done by first writing a function routine that accepts X to return Y_{opt}, which then is called in the routine for iteratively solving $Y_{\text{opt}}(X^*) = X^*$.

S.1 Density-dependent mortality

One of the easiest twist to the SIR model is to assume that the background mortality rate, μ, is a function $\mu(N)$ of the total population size $N = S + I + R$. For instance, one may choose $\mu = \mu_0 + \kappa N$, where κ measures the strength of density-dependence. In an uninfected population, we have $N = S_0$, the density of susceptible individuals in the absence of disease, and therefore the basic reproduction ratio of a pathogen with traits X arising in the uninfected population is

$$R_0(X) = \frac{\beta(X)}{\mu_0 + \kappa S_0 + \alpha(X) + \gamma} S_0 \tag{S1}$$

(where for simplicity only transmission and virulence are assumed to depend on the traits X). In contrast, the basic reproduction ratio of a mutant pathogen with traits Y in the environment produced by a resident pathogen strain with traits X is

$$\mathcal{R}(Y|\hat{E}(X)) = \frac{\beta(Y)}{\mu_0 + \kappa \hat{N}(X) + \alpha(Y) + \gamma} \hat{S}(X) = \frac{\beta(Y)}{\mu_0 + \kappa N_0 + \alpha(Y) + \gamma + \delta(\hat{E})} \hat{S}(X) \tag{S2}$$

with $N_0 = S_0$ and $\delta(\hat{E}) = \kappa(\hat{N}(X) - S_0)$ the additional effect of the environmental feedback loop on mortality compared to the mortality term in R_0. For a concave transmission-virulence trade-off $\beta(\alpha)$, a graphical construction allows us to visualise the effect of the environmental feedback on the ESS compared to the prediction of R_0 maximisation. To see how, note that, by differentiating $\mathcal{R}$ with respect to Y and evaluating the result at $Y = X$, potential ESS's must satisfy the following equation

$$\frac{\mathrm{d}\beta}{\mathrm{d}\alpha}(\alpha^*) = \frac{\beta(\alpha^*)}{\mu_0 + \kappa S_0 + \alpha^* + \gamma + \delta(\hat{E}(\alpha^*))} \tag{S3}$$

The tangent at the ESS to the trade-off curve must thus go through the point A $(-\mu_0 - \kappa S_0 - \gamma - \delta(\hat{E}), 0)$, whereas for R_0 maximisation the tangent goes through the point $(-\mu_0 - \kappa S_0 - \gamma, 0)$. Then, $\delta(\hat{E})$ is the length of the OA segment in figure 1C in the main text. If the presence of the parasite leads to a decrease in the density of hosts (such that $\hat{N}(X) - S_0 < 0$), the point A is to the right of O, and the ES virulence is lower than the value that maximises R_0.

Deeper analyses of this scenario can be found in the literature (Andreasen and Pugliese, 1995, Pugliese, 2002, Dieckmann and Metz, 2006, Svennungsen and Kisdi, 2009).

S.2   Superinfection models

Superinfection models May and Nowak (1994), Adler and Mosquera Losada (2002) assume that a host infected by a pathogen strain can be infected by another strain, which, with a certain probability, can oust the resident strain on a fast time scale compared to the time scale of transmission. The baseline SIR model can be extended to include superinfection, in which case the density of hosts infected by a mutant strain m satisfies the following differential equation (under the assumption that only one other strain, r, is present in the population):

$$\frac{\mathrm{d}I_m}{\mathrm{d}t} = (\beta_m I_m)S - (\mu + \alpha_m + \gamma)I_m - \underbrace{(\sigma_{rm}\beta_r I_r)}_{h_r} I_m + \underbrace{(\sigma_{mr}\beta_m I_m)}_{h_m} I_r. \tag{S4}$$

The first term represents the production of new hosts infected by the mutant strain from uninfected hosts; the second term represents the removal of I_m hosts due to mortality and recovery; the third term gives the loss of I_m hosts due to superinfection by the resident strain (with superinfection probability σ_{rm}); and the fourth term gives the production of new I_m hosts due to the superinfection of hosts infected by the resident strain. The quantities h_r and h_m are the forces of infection by resident and mutant strains respectively.

Note that superinfection is a meaningful process only if the pathogen population is dimorphic. If only a single pathogen is present, the model collapses to the baseline SIR model (and therefore the epidemiological R_0 for the superinfection model is the same as in the SIR model).

Assuming that the resident population is at the equilibrium $(\hat{S}, \hat{I}_r)$ and that the mutant strain is rare, the mutant strain will invade if $(1/I_m)\mathrm{d}I_m/\mathrm{d}t > 0$, which can be cast in the form of a basic reproduction ratio (Gandon et al., 2001a):

$$\mathcal{R}' = \frac{\beta_m}{\mu + \alpha_m + \gamma + \sigma_{rm}\beta_r \hat{I}_r}(\hat{S} + \sigma_{mr}\beta_r \hat{I}_r) > 1 \tag{S5}$$

In the following, we assume that $\beta_m = \beta(\alpha_m)$ and $\beta_r = \beta(\alpha_r)$. Under the (rather unrealistic) assumption that the probabilities of superinfection are independent of the traits, differentiating with respect to α_m leads to the following condition at the ESS:

$$\frac{\mathrm{d}\beta}{\mathrm{d}\alpha}(\alpha^*) = \frac{\beta(\alpha^*)}{\mu + \alpha^* + \gamma + \sigma_{rm}\beta(\alpha^*)\hat{I}_r(\alpha^*)} \tag{S6}$$

in accordance with the Marginal Value Theorem (Charnov, 1976). When $\sigma_{rm} = 0$, the right-hand side is the basic reproduction ratio R_0 divided by S_0 and, for a concave trade-off $\beta(\alpha)$, the model admits an ESS which coincides with the value of virulence that maximises R_0. When $\sigma_{mr} > 0$, the additional term in the denominator, which is simply the force of infection exerted by resident parasites on hosts infected by the mutant strain, gives the length of the OA segment in figure 1B in the main text. Because the force of infection is positive, the ESS virulence is predicted to be higher than the value that maximises R_0.

The assumption of trait-independent take-over probabilities may make little biological sense, but has the didactical value of showing that superinfection can affect the ESS purely through the indirect effects of the environmental feedback loop, without any within-host competitive asymmetries! More realistically, the superinfection probabilities σ_{rm} and σ_{mr} will be function of the traits. A common assumption in the literature is that $\sigma_{ij} = s(\alpha_i - \alpha_j)$, that is the probability of superinfection depends on the difference in virulence between the two strains. In that case, differentiating $\mathcal{R}'$ with respect to α_m leads to another condition than equation (S6) (see e.g. Gandon et al. (2001a), Boldin and Diekmann (2008), Boldin et al. (2009)). We obtain

$$\frac{\mathrm{d}\beta}{\mathrm{d}\alpha}(\alpha^*) = \frac{\beta(\alpha^*)(1 - 2h^*s'(0))}{\mu + \alpha^* + \gamma + h^*s(0)} \tag{S7}$$

where $h^* = \beta(\alpha^*)\hat{I}(\alpha^*)$ is the force of infection due to resident parasites (Gandon et al., 2001a). A graphical representation can be found by noting that the tangent line at the ESS goes through a point
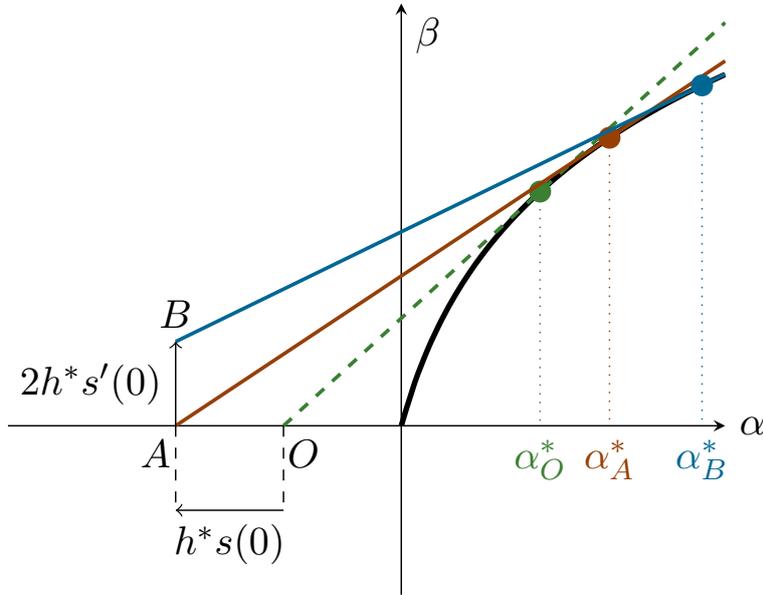
Figure S2: Graphical representation of the effect of within-host competitiveness in the superinfection model

B that is obtained by raising point A vertically by $2h^*s'(0)$ (figure S2, Gandon et al. (2001a)). It can then be seen that, when superinfection depends on a within-host competitiveness that increases with virulence, selection favours even higher virulence (compare α_B^* and α_A^*).

S.3   Limited cross-immunity

The baseline SIR model assumes that recovery to one strain confers immunity to all other strains. However, cross-immunity is far from perfect in nature. Limited cross-immunity makes the recovered class vulnerable to new infections. We assume that the susceptibility of the R class to new infections is a function of the virulence. Specifically, we suppose that a mutant pathogen with virulence α' will be able to infect hosts that have recovered from an infection by a resident pathogen with virulence α with probability $1 - c(\alpha', \alpha)$, where $c(\alpha', \alpha)$ is a measure of cross-immunity. Full cross-immunity is equivalent to $c = 1$. We also assume that $c(\alpha, \alpha) = 1$ and that the derivative of c with respect to its first argument is zero, which follows from the reasonable assumptions that the cross-immunity decreases with increased dissimilarity between the traits.

With these assumptions, we have the following fitness proxy

$$\mathcal{R}' = \frac{\beta'}{\mu + \alpha' + \gamma'}(\hat{S} + (1 - c(\alpha', \alpha))\hat{R}) \tag{S8}$$

The full analysis of this model is still a work in progress (Metz & Boldin, in prep) but we give here a rough sketch of one of the most salient results. We first make some notational changes to simplify the argument, and write α, β, γ as $\alpha(x), \beta(x), \gamma(x)$, α', β', γ' as $\alpha(y), \beta(y), \gamma(y)$, $\mathcal{R}' = \mathcal{R}(y, x)$, and $c(\alpha', \alpha)$ as $c(y, x)$. In the case of functions of more variables like c we indicate the position at which we differentiate with an index, e.g. c_1' for partial differentiation for the first argument, etc.

The condition $\mathcal{R}(y, x) := \mathcal{R}(y|\hat{E}(x)) > 1$ is equivalent to $s(y, x) > 0$ with

$$s(y, x) = \beta(y)[\hat{S}(x) + (1 - c(y, x))\hat{R}(x)] - (\mu + \alpha(y) + \gamma(y)) = (\mu + \alpha(y) + \gamma(y))[\mathcal{R}(y, x) - 1] \tag{S9}$$

Differentiating $s(y, x)$ with respect to y, and evaluating the result at $y = x$, we obtain the following expression for the selection gradient

$$\begin{aligned} s_1'(x, x) =& \beta'(x)[\hat{S}(x) + (1 - c(x, x))\hat{R}(x)] - \beta(x)c_1'(x, x)\hat{R}(x) - (\alpha'(x) + \gamma'(x)) \\ =& \beta'(x)\hat{S}(x) - (\alpha'(x) + \gamma'(x)) \end{aligned} \tag{S10}$$

where the second line follows from the assumptions $c(x,x) = 1$ and $c'_1(x,x) = 0$. The zeros of $s'_1(x,x)$ are the evolutionary singularities. Since (S10) has exactly the same form as in the ordinary SIR model, under the usual trade-off assumptions the evolutionarily singular point x^* maximises R_0. If we assume x to be a scalar such that β, α and γ increase in x, the sign structure of the selection gradient around zero shows that x^* attracts. The only difference with the SIR model is that x^* need not maximise $\mathcal{R}(y, x^*)$ for y. In other words, the singular point may also be a branching point, depending on the values of the parameters that are not under evolutionary control.

S.4 Vertical vs horizontal transmission

For a parasite with both vertical and horizontal transmission, a slight modification of the SIR model (Ferdy and Godelle, 2005) leads to the following equation for the dynamics of hosts infected by a rare mutant pathogen in a resident population at equilibrium:

$$\frac{\mathrm{d}I'}{\mathrm{d}t} = \beta'\hat{S}I' + \epsilon b'_I(\hat{N})I' - (\mu + \alpha' + \gamma)I' \tag{S11}$$

The second-term gives the contribution of infected offspring to the dynamics of I'. This contribution is equal to the probability of vertical transmission, ϵ, times the birth rate of hosts infected by the mutant pathogen, $b'_I(\hat{N})$, which is assumed to be a function of the total host density, $\hat{N}$, times the density of hosts infected by the mutant pathogen, I'. The invasion condition can then be cast into the form

$$\mathcal{R}' = \frac{\beta'\hat{S} + \epsilon b'_I(\hat{N})}{\mu + \alpha' + \gamma}. \tag{S12}$$

A similar reasoning for a pathogen in an uninfected population leads to the expression of R_0

$$R_0 = \frac{\beta S_0 + \epsilon b_I(S_0)}{\mu + \alpha + \gamma}. \tag{S13}$$

For a transmission-virulence trade-off $\beta(\alpha)$, the value of α that maximises R_0 satisfies

$$\frac{\mathrm{d}\beta}{\mathrm{d}\alpha}(\alpha) = \frac{\beta(\alpha) + \epsilon\frac{b_I(S_0)}{S_0}}{\mu + \alpha + \gamma}. \tag{S14}$$

A graphical construction can be obtained by noting that this means that the tangent at the ESS goes through a point O' obtained from O by a vertical translation of $-\epsilon b_I(S_0)/S_0$ (figure S3).

The ESS can be calculated from the expression of $\mathcal{R}'$. Writing $\beta' = \beta(\alpha')$ and writing $\mathcal{R}'$ as a function $\mathcal{R}(\alpha', \alpha)$, we can differentiate $\mathcal{R}(\alpha', \alpha)$ with respect to α' and evaluate the result at $\alpha' = \alpha$. Potential ESS will be zeros of the resulting function of α and will therefore satisfy the following condition

$$\frac{\mathrm{d}\beta}{\mathrm{d}\alpha}(\alpha) = \frac{\beta(\alpha) + \epsilon\frac{b_I(\hat{N}(\alpha))}{\hat{S}(\alpha)}}{\mu + \alpha + \gamma} \tag{S15}$$

which shows that the picture for the determination of the ESS differs from that for R_0 maximisation by a change in the amount that O is lowered, $\epsilon(b_I(\hat{N}(\alpha))/\hat{S}(\alpha) - b_I(S_0)/S_0)$. In general, both $\hat{N}(\alpha)$ and $\hat{S}(\alpha)$ will be lower than S_0. However, we may expect b_I to be a decreasing function of density, so that in the ESS case the point where the tangent line touches the trade-off curve will come out lower, and hence the ESS value of α will be lower than the value obtained from R_0 maximisation. As in the other cases, the magnitude of the effect will be inversely proportional to the curvature of β.

Note that, in this model, the ESS condition can be simplified further by using the fact that $\mathcal{R}(\alpha, \alpha) = (\beta(\alpha)\hat{S}(\alpha) + \epsilon b_I(\hat{N}(\alpha)))/(\mu + \alpha + \gamma) = 1$, which leads to $\mathrm{d}\beta/\mathrm{d}\alpha = 1/\hat{S}(\alpha)$. This is the same condition as the SIR model with only horizontal transmission, but the expression for $\hat{S}(\alpha)$ is different due to the effect of vertical transmission.
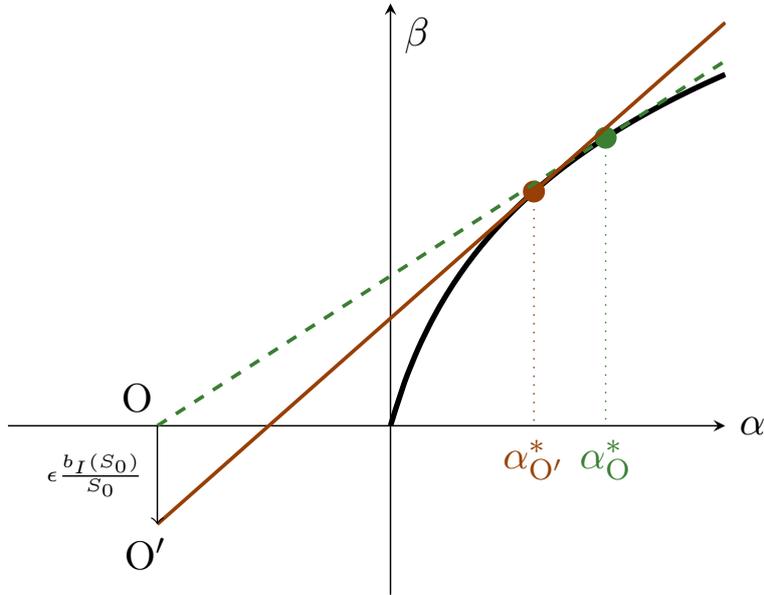
Figure S3: Graphical representation of R_0 maximisation in the model with both vertical and horizontal transmission, compared with the case with only horizontal transmission.

S.5 Multi-host parasites

We return to our baseline SIR model, but now assume that the host populations consists of two types (or classes, or species), labelled 1 and 2. Consider first that the host population is infected by a single resident parasite strain. At endemic equilibrium, the population is characterised by equilibrium densities $\hat{S}_1$ and $\hat{S}_2$ for uninfected hosts, and $\hat{I}_1$ and $\hat{I}_2$ for infected hosts. In this resident population, hosts infected by a new mutant parasite (with densities I'_1 and I'_2) will have the following dynamics when the mutant strain is rare:

$$\frac{\mathrm{d}I'_1}{\mathrm{d}t} = \beta'_{11}\hat{S}_1 I'_1 + \beta'_{21}\hat{S}_1 I'_2 - (\mu + \alpha'_1 + \gamma)I'_1, \tag{S16}$$

$$\frac{\mathrm{d}I'_2}{\mathrm{d}t} = \beta'_{22}\hat{S}_2 I'_2 + \beta'_{12}\hat{S}_2 I'_1 - (\mu + \alpha'_2 + \gamma)I'_2, \tag{S17}$$

where β'_{ij} is the transmission rate of the mutant parasite from host type i to host type j, and α'_i is the virulence of the mutant parasite in host type i (the resident strain similarly has parameters β_{ij} and α_i). The equations for I'_1 and I'_2 can also be written in matrix form

$$\frac{\mathrm{d}}{\mathrm{d}t}\begin{pmatrix} I'_1 \\ I'_2 \end{pmatrix} = \begin{pmatrix} \beta'_{11}\hat{S}_1 - (\mu + \alpha'_1 + \gamma) & \beta'_{21}\hat{S}_1 \\ \beta'_{12}\hat{S}_2 & \beta'_{22}\hat{S}_2 - (\mu + \alpha'_2 + \gamma) \end{pmatrix}\begin{pmatrix} I'_1 \\ I'_2 \end{pmatrix} \tag{S18}$$

The Next-Generation Theorem (Diekmann et al., 1990, Hurford et al., 2010) can be used to compute the invasion fitness of the mutant strain in such structured populations. Doing so leads to the following expression for the pathogen fitness (Gandon, 2004),

$$\mathcal{R}' = \frac{\beta'_{11}\hat{S}_1}{2(\mu + \alpha'_1 + \gamma)} + \frac{\beta'_{22}\hat{S}_2}{2(\mu + \alpha'_2 + \gamma)}$$
$$+ \sqrt{\left(\frac{\beta'_{11}\hat{S}_1}{2(\mu + \alpha'_1 + \gamma)} + \frac{\beta'_{22}\hat{S}_2}{2(\mu + \alpha'_2 + \gamma)}\right)^2 + \frac{\beta'_{12}\beta'_{21} - \beta'_{11}\beta'_{22}}{(\mu + \alpha'_1 + \gamma)(\mu + \alpha'_2 + \gamma)}\hat{S}_1\hat{S}_2} \tag{S19}$$

Two extreme cases can be deduced from this general formula. First, when there is no transmission bias between host types, such that $\beta'_{12}\beta'_{21} - \beta'_{22}\beta'_{11} = 0$, the invasion fitness reduces to (Gandon, 2004)

$$\mathcal{R}' = \frac{\beta'_{11}\hat{S}_1}{\mu + \alpha'_1 + \gamma} + \frac{\beta'_{22}\hat{S}_2}{\mu + \alpha'_2 + \gamma}. \tag{S20}$$

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This is the case discussed in Box 4 in the main text. Each host can then be viewed as a separate transmission pathway for the parasite.

Second, when the pathogen has to alternately exploit the two host types, as in vector-borne diseases, we have $\beta'_{11} = \beta'_{22} = 0$, and the invasion fitness takes the following form (Gandon, 2004)

$$\mathcal{R}' = \sqrt{\frac{\beta'_{12}\beta'_{21}}{(\mu + \alpha'_1 + \gamma)(\mu + \alpha'_2 + \gamma)}\hat{S}_1\hat{S}_2} \tag{S21}$$

Note that, by a similar reasoning, the basic reproduction ratio of the mutant parasite in an uninfected host population will be

$$R'_0 = \sqrt{\frac{\beta'_{12}\beta'_{21}}{(\mu + \alpha'_1 + \gamma)(\mu + \alpha'_2 + \gamma)}\hat{S}_{0,1}\hat{S}_{0,2}} = \sqrt{R'_{0,1}R'_{0,2}} \tag{S22}$$

where $S_{0,i}$ is the density of type-i hosts in the population in the absence of parasites, $R_{0,1} = \beta_{12}S_{0,2}/(\mu + \alpha_1 + \gamma)$ is the "basic reproduction ratio" in host 1, and $R_{0,2}$ has a similar interpretation and expression after permutation of the indices 1 and 2.

It follows that

$$\mathcal{R}' = R'_0\sqrt{\frac{\hat{S}_1\hat{S}_2}{S_{0,1}S_{0,2}}}. \tag{S23}$$

Hence, condition (5) in the main text is satisfied, and R_0 is an optimisation principle, with $\phi = \sqrt{(\hat{S}_1\hat{S}_2)/(S_{0,1}S_{0,2})}$ as a matching pessimisation principle.

S.6 Spatially structured populations

We now turn to a spatial extension of the SIR model, where transmission takes place according to a specific infection kernel (for instance, one may consider infection to nearest neighbours in network-based models, or a distance-dependent kernel in spatially explicit models). In a pathogen-free population, we can calculate $R_0(X)$ as

$$R_0(X) = \frac{\beta[S|I]_0}{\mu + \alpha + \gamma}$$

where $[S|I]_0$ can be calculated during the initial invasion phase using a quasi-equilibrium assumption for the local infection patterns, following Keeling (1999). In general, $R_0(X)$ is reduced in spatial models compared to non-spatial models, because pathogens tend to have access to a reduced number of susceptible contacts (Keeling, 1999).

In a resident population at equilibrium, the invasion fitness of a rare mutant strain is $\rho(Y|\hat{E}) = \beta'[S|I'] - (\mu + \alpha' + \gamma)$, where $[S|I']$ is also calculated at quasi-equilibrum (van Baalen and Rand, 1998, Ferrière and Le Galliard, 2001, Lion, 2016). It follows that the mutant invades if

$$[S|I'] - \frac{\mu + \alpha' + \gamma}{\beta'} > 0$$

and because at resident equilibrium we have $\widehat{[S|I]} = (\mu + \alpha + \gamma)/\beta$, the invasion condition can be written as

$$\frac{[S|I'] - \frac{\mu+\alpha'+\gamma}{\beta'}}{[S|I']_0} > \frac{\widehat{[S|I]} - \frac{\mu+\alpha+\gamma}{\beta}}{[S|I]_0}$$

or equivalently as

$$\left(\frac{1}{R_0(X)} - \frac{1}{R_0(Y)}\right) + \left(\frac{[S|I']}{[S|I']_0} - \frac{\widehat{[S|I]}}{[S|I]_0}\right) > 0. \tag{S24}$$

This shows that only if the second term is proportional to the first can the outcome of evolution be predicted by maximising $R_0(X)$. The difference with inequality (12) in the main text is that the first

term depends on the *spatial* basic reproduction ratios, which are lower than the non-spatial ones, while the second term measures the difference in the access to susceptible hosts between the mutant and resident strains, measured relative to the initial structure of an invading pathogen population in an otherwise pathogen-free population.

Analysing the effect of the mutation on this second term has been the focus of many works (reviewed in Lion and Gandon (2015); see e.g. Boots and Sasaki (1999), Lion and Boots (2010) for a sample of primary analyses). To make a long story short, it can be shown in network-based models that this term depends on the balance between genetic structure (measured by the genetic relatedness r between neighbouring parasites) and some measure of the epidemiological structure of the resident host population, e. This observation provides another intuition for why $R_0(X)$ cannot be maximised by selection in spatially structured populations: Because $R_0(X)$ by definition cannot take into account the between-host genetic structure of the pathogen population, it cannot properly serve as a measure of inclusive fitness, as needed for computing the effect of selection in space (Lion and Boots, 2010).

As shown in Lion and Boots (2010), condition (S24) can then be cast in a Marginal Value form, which leads to a graphical representation similar to figure 1C in the main text. The key result is then that, provided that $r > e$, selection will favour less virulent parasites in spatially structured host populations. Note however that the model may yield the opposite prediction if a mixture of long-range and short-range transmission is allowed (Kamo et al., 2007, Lion and Boots, 2010).

S.7   Non-equilibrium dynamics

Traditionally, R_0 is only considered for non-fluctuating environments. However, over the past ten years the concept has been extended to ever more complicatedly fluctuating environments such as periodic (Bacaër and Guernaoui, 2006, Bacaër and Ait Daids, 2012) or random ones (Bacaër and Khaladi, 2013). Unfortunately, these general R_0's are difficult to calculate except for unstructured populations, in which case they just equal the ratio of the time averages of the birth and death rates (Bacaër and Guernaoui, 2006, Bacaër and Khaladi, 2013).

For periodically fluctuating environments, superficially similar models have been found to make different predictions for the evolution of pathogen life-history traits. For instance, van den Berg et al. (2011) considered a model such that pathogen evolution could be predicted by maximising $R_0(X)$, while a similar model by Hamelin et al. (2011) predicts evolutionary diversification of the pathogen population. This shows that even in complicated models sometimes R_0 maximisation can do the job, but that one should not uncritically rely on this being the case.

S.8   Sensitivity of the ESS virulence to environmental feedbacks

Till now we for didactical reasons looked at the models with a more complicated environmental feedback loop as modifications of the simple SIR model. For the same reason we looked at the quantitative effects of the added complication by gauging the outcome of a full ESS calculation against the outcome of the more familiar and mathematically simpler R_0 maximisation. Below we will take a methodological more correct perspective and ask ourselves how large the error is that we make if we instead of doing an ESS calculation would naively maximise R_0. The additional advantage of this perspective is that the outcome of the ESS calculation, and with that $\hat{E}$ in $\delta(\hat{E})$, can be considered as known, whereas in the earlier naive perspective we still have to take account of the fact that the quantity $\hat{E}$ itself still depends on the value of α_A^* that we seek to determine. In the new perspective we thus start from a known α_A^* and $\delta(\hat{E})$ and compare this with the α_O^* that we get when we set $\delta(\hat{E}) = 0$. This does not change any of the graphs, but it leads to different, easier, calculations.

A suitable reinterpretation of the graphical argument from the main text heuristically indicates that the effect of removing the term $\delta(\hat{E})$ is in some way inversely proportional to the curvature of the trade-off. Here we give a formal mathematical argument. In order to do calculations we have to keep our analysis local. (In this context it should be noted that the rigorous concept of curvature is also local. The seemingly global character of our graphical argument comes from the suggestion that we

can use the term in a larger scale averaged sense. This suggestion may feel right but so-far is without a rigorous underpinning.)

We focus on the case where $\mathcal{R}(\alpha|\hat{E})$ can be written as $\frac{\beta(\alpha)}{\mu^*+\gamma+\alpha}\hat{S}$, with $\mu^* = \mu(E_0) + \Delta_\mu$, and blandly assume Δ_μ to be small. The corresponding α_A^*, which from now on shall just call α^*, satisfies:

$$\frac{\mathrm{d}}{\mathrm{d}\alpha}\mathcal{R}(\alpha|\hat{E})\big|_{\alpha=\alpha^*} = \frac{\beta'(\alpha^*)(\mu^*+\gamma+\alpha^*) - \beta(\alpha^*)}{(\mu^*+\gamma+\alpha^*)^2}\hat{S} = 0 \qquad \Leftrightarrow \qquad \beta(\alpha^*) = \beta'(\alpha^*)(\mu^*+\gamma+\alpha^*)$$

with a prime now indicating differentiation. Differentiating the right equality for μ^* gives

$$\beta'(\alpha^*)\frac{\mathrm{d}\alpha^*}{\mathrm{d}\mu^*} = \beta''(\alpha^*)\frac{\mathrm{d}\alpha^*}{\mathrm{d}\mu^*}(\mu^*+\gamma+\alpha^*) + \beta'(\alpha^*)\left(1+\frac{\mathrm{d}\alpha^*}{\mathrm{d}\mu^*}\right).$$

Solving for $\mathrm{d}\alpha^*/\mathrm{d}\mu^*$ gives

$$\frac{\mathrm{d}\alpha^*}{\mathrm{d}\mu^*} = \frac{-\beta'(\alpha^*)}{\beta''(\alpha^*)(\mu^*+\gamma+\alpha^*)} = \frac{-\beta(\alpha^*)}{\beta''(\alpha^*)(\mu^*+\gamma+\alpha^*)^2}.$$

So, the sensitivity to an additional term in the numerator is inversely proportional to the curvature of the trade-off at α^*, with a proportionality constant that does depend on the trade-off only in so far as the latter co-determines α^* and $\beta(\alpha^*)$. The dependence on the curvature of the trade-off we already knew from Figure 1 in the main text. The precise form of the proportionality constant is new.

Note that for small Δ_μ the difference between the curvature of the trade-off at α_A^* and α_O^* is only $O(\Delta_\mu)$, so that to the considered order of approximation they are interchangeable.

The graphical constructions tell that similar arguments should apply to the superinfection models in S2 and the mixed transmission model in S4.

S.9 On myxomatosis

After introduction of a virulent (Grade I) strain of the myxoma virus in Australia, virulence quickly dropped and settled to a value corresponding approximately to the Grade III strain from 1958 to 1980 (although with an increasing trend). During that period of time, resistance in the rabbit population rose, and this led to a further increase in virulence from 1980 onwards (figure S4a; Fenner and Fantini (1999)).

When Anderson and May (1982) analysed this data, they computed R_0 as $\beta S_0/(\mu+\alpha+\gamma)$ using an empirically established trade-off between virulence and recovery ($\gamma(\alpha) = -0.032 - 0.0129\ln(\alpha)$), but kept the transmission rate constant (arbitrarily assuming $\beta S_0 = 0.2$ day^{-1}). The resulting R_0 is plotted as the red dashed curve in figure S4c. Compared to the distribution of virulence for the period 1975-1981, the value of virulence that maximises R_0 is too low. Massad (1987) refined Anderson and May (1982)'s analysis using an empirical relationship between transmission and virulence (plotted in figure S4b). Using both the transmission-virulence and virulence-recovery trade-off, he showed that R_0 maximisation then provided a better fit to the observed distribution of virulence (figure S4c, plain blue curve). Interestingly, while reanalysing this data, we also found that removing the recovery-virulence trade-off had little effect on the prediction (figure S4c, dashed blue curve, where the constant value $\gamma = 0.02$ is used), which suggests that the transmission-virulence trade-off is the main force shaping R_0 maximisation.

Assuming that the classical expression of R_0 is indeed suitable to describe the epidemiological dynamics of the myxoma virus-rabbit system, this example shows that the evolutionary dynamics of the myxoma virus in Australia is characterised by two phases. In a first phase, evolution appears to drive the population close to the value that maximises R_0. This seems consistent with our analysis in Appendix S.8, which shows that the ESS will not deviate much from the value maximising R_0 for a highly concave transmission-virulence trade-off as depicted in figure S4b, provided the environmental feedbacks only affect the duration of the infection. In a second phase, however, host heterogeneity due to the rise of resistance led to a more complex environmental feedback loop and caused virulence to increase. If R_0 maximisation occurs in this system, it is thus only transiently.
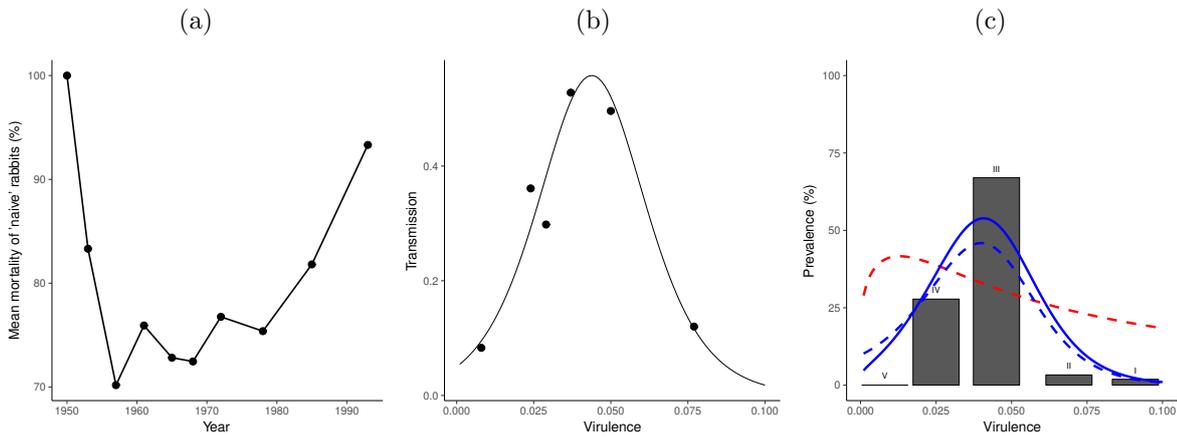
Figure S4: (a) Mean virulence as a function of time during the myxomatosis epidemic in Australia. (b) Transmission-virulence trade-off (fit vs data), redrawn from Massad (1987). (c) Strain distribution between 1975 and 1981 (the bars indicate the frequencies of the five virulence grades I to V), and R_0 computed for various assumptions on the transmission-virulence and recovery-virulence trade-offs (see text for more details). Note that the vertical scale is arbitrary for R_0, since what matters here is the predicted value of virulence that maximises the function.

S.10   On HIV

There are two points in our discussion of Fraser et al. (2007)'s work that may require some explanation.

The first, rather finicky, point is that the data on which the estimation of R_0 in Fraser et al. (2007) were based came from 1982-1993. At that time the main behavioural changes in the wake of HIV awareness had already occurred. Since these changes are not under the parasite's hereditary control, in our set-up they by definition count as changes in its environment caused by the disease. So what Fraser et al. (2007) calculated strictly speaking was not the expected number of secondary infections caused by a single freshly infected in an as yet uninfected population. From the point of view of the environment created by it the epidemic was already well under way.

The second point concerns the various time scales. The HIV epidemic at that time and even now clearly is still in a transient stage, instead of in an endemic equilibrium. However, as epidemics go, the HIV one unfolds very slow, whereas the HIV virus evolves very fast, due to the virus' highly unfaithful reproduction, and thus may be expected evolutionarily to keep up well with any further environmental changes caused by the epidemic.

A confounding point here is that the arguments underlying the ESS calculations as put forward by us (and therefore also the derived R_0 maximisation paradigm in the cases where it is justified by the nature of the environmental feedback loop) consider only one mutant at a time, that is, are implicitly based on an assumption of mutation limitation. However, ESS calculations are generally very robust against deviations from this assumption. What really matters is that the mutants have positive (negative) fitness whenever they would have that in a homogeneous population of a representative mutant in the mutant swarm.

We thus guess that these are the actual reasons why the measured "R_0" was found to be optimal: the HIV population closely tracks a moving optimum of $\mathcal{R}(Y|E(t))$, with $E(t)$ the current environment.