Evolutionary suicide through a non-catastrophic bifurcation: adaptive dynamics of pathogens with frequency-dependent transmission*

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Abstract

Evolutionary suicide is a riveting phenomenon in which adaptive evolution drives a viable population to extinction. Gyllenberg and Parvinen (Bull. Math. Biol. 63: 981-993, 2001) showed that, in a wide class of deterministic population models, a discontinuous transition to extinction is a necessary condition for evolutionary suicide. An implicit assumption of their proof is that the invasion fitness of a rare strategy is well-defined also in the extinction state of the population. Epidemic models with frequency-dependent incidence, which are often used to model the spread of sexually transmitted infections or the dynamics of infectious diseases within herds, violate this assumption. In these models, evolutionary suicide can occur through a non-catastrophic bifurcation whereby pathogen adaptation leads to a continuous decline of host (and consequently pathogen) population size to zero. Evolutionary suicide of pathogens with frequency-dependent transmission can occur in two ways, with pathogen strains evolving either higher or lower virulence.

Keywords: adaptive dynamics, evolutionary suicide, non-catastrophic bifurcation, transcritical bifurcation, extinction, virulence, frequency-dependent incidence

Mathematics Subject Classification (2010): 92D15 92D30 92D40

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1   Introduction

A naive view of evolution holds that natural selection, 'the survival of the fittest', will always improve a species, making it ever better adapted to its environment. This naive view is however false. As highlighted by Gyllenberg (2008), evolutionary suicide, the phenomenon of natural selection leading to the very extinction of the population, starkly proves that natural selection is not for the best of the species.

Gyllenberg et al. (2002) showed that in a structured metapopulation model with evolving dispersal, a bifurcation leading to a discontinuous transition to extinction is a necessary condition for evolutionary suicide to occur. In a follow-up paper, Gyllenberg and Parvinen (2001) extended this result to a wide class of deterministic models. It is now widely accepted that evolutionary suicide cannot happen through a continuous transition to extinction at a finite trait value (Parvinen and Dieckmann (2013); Rankin and López-Sepulcre (2005); Webb (2003)), although examples are known of gradual decline towards extinction as the trait value becomes infinite (Matsuda and Abrams (1994); Webb (2003)).

It is well known that an epidemic can drive the host population extinct if incidence is frequency-dependent (i.e. if the rate of contacts a specific host individual has with other hosts is constant) (Getz and Pickering (1983); Boots and Sasaki (2003); Diekmann et al. (2012)). By contrast, epidemic models with density-dependent incidence (where the contact rate is assumed to be proportional to the host population size) typically do not predict deterministic disease-driven population extinctions (but such extinctions are possible when Allee effects are considered (Hilker et al. (2009); Gandon and Day (2009)). Frequency-dependent incidence (also called standard incidence (Allen (2007))) is a good approximation of the spread of sexually transmitted diseases, because mates seek each other out even if population density is low and therefore random encounters are rare (Getz and Pickering (1983)). It is also believed to be a suitable description of infection process in vector-borne diseases (where relatively large vector populations and changes in vector behaviour may compensate for variations in host density (Antonovics et al. (1995); Thrall et al. (1995))) and for infections among animals in herds (which occupy an area proportional to the number of individuals, such that small herds concentrate in a small area keeping the contact rate constant (de Jong et al. (1995); Diekmann et al. (2012))).

The question we pose here is simple: starting with a viable host-pathogen system in which transmission is frequency-dependent, can the pathogens evolve in such a way that they drive their hosts (and therefore themselves) to extinction? If so, what is the nature of the bifurcation leading to evolutionary suicide?

Boots and Sasaki (2003) investigated the evolution of pathogen transmission and virulence under frequency-dependent incidence in a simple optimization model, and found that the pathogen may evolve such that it drives the system extinct. Their study did not focus on the type of bifurcation leading to extinction, but the simple structure of the model suggests that extinction happens as population size declines to zero continuously. This is in apparent contradiction with the results of Gyllenberg and Parvinen (2001); Gyllenberg et al. (2002).

In this paper, we show that adaptive dynamics of pathogen virulence can lead to

evolutionary suicide through a non-catastrophic bifurcation in a rather general family of SI models with frequency-dependent incidence. For didactical purposes, we start by introducing a relatively simple family of autonomous SI models, determine the condition for evolutionary suicide with evolving pathogen virulence and argue that, if evolutionary suicide occurs, it occurs via a continuous transition to extinction. We reconcile this with the results of Gyllenberg et al. (2002); Gyllenberg and Parvinen (2001) by arguing that epidemic models with frequency-dependent incidence violate an implicit assumption of Gyllenberg et al. (2002); Gyllenberg and Parvinen (2001), thereby allowing for a new route to evolutionary suicide. We proceed by analyzing in more detail two specific toy models. These models show that evolutionary suicide can occur via two different routes: extinction may be the consequence of evolution towards either more or less virulent strains. The latter, less intuitive route may happen because as the infectious lifetime of an infected host is prolonged with decreased virulence, the prevalence of the disease increases and the host population birth rate may decline to the extent that the population is no longer viable. Evolution to self-extinction may in fact occur in more involved systems that include arbitrary population dynamics, pathogens with arbitrary effects on the birth and death rates of the host and on the way the host interacts with its environment, and non-autonomous dynamics where the birth and death rates fluctuate in time. We demonstrate this in Appendix A, thereby generalizing the results of Boots and Sasaki (2003). We conclude the main part of the paper with a discussion.

2 SI epidemics with frequency-dependent transmission

We consider an SI model with frequency-dependent incidence described by the differential equations

$$
\begin{aligned}
\frac{dS}{dt} &= b_S(N, x)S + b_I(N, x)I - \mu(N)S - \beta(\alpha)\frac{SI}{N} \\
\frac{dI}{dt} &= \beta(\alpha)\frac{SI}{N} - \mu(N)I - \alpha I.
\end{aligned}
\tag{1}
$$

Here S and I denote, respectively, the density of susceptible and infected (as well as infectious) hosts. $N = S + I$ is the total host population density, and $x = S/N$ is the fraction of susceptible hosts. The per capita birth rates of susceptibles and infecteds, b_S and b_I, respectively, depend on the fraction of susceptibles or on the total population density (see details below in Model I and Model II). The per capita background mortality rate is denoted by μ. We assume that μ is a non-decreasing function of N; for example, when population densities become higher the resources become more scarce, leading to increased host mortality. The transmission rate $\beta(\alpha)$ increases with virulence (i.e. the disease-induced death rate), α, according to the classic transmission-virulence trade-off hypothesis (Anderson and May (1982)). In Appendix A, we consider a much more general model and show that evolutionary suicide can happen independently of many details incorporated in (1).

The important assumption of this model in view of evolutionary suicide is that incidence is frequency-dependent, i.e., a susceptible host encounters a fixed number of other hosts per unit of time, the fraction I/N of them being infected. Frequency-dependent incidence is routinely assumed for sexually transmitted diseases (e.g. Thrall et al. (1993); Thrall and Antonovics (1997); Boots and Sasaki (2003); Berec and Maxin (2013); Bernhauerová and Berec (2015)). It is also believed to be a suitable description of infection process among animals in herds (Diekmann et al. (2012); de Jong et al. (1995)) and in vector-borne diseases (Thrall et al. (1993); Antonovics et al. (1995); Thrall et al. (1995)). We elaborate more on this assumption in the Discussion.

Due to the singularity of (1) at $S = I = 0$, we rewrite the system in terms of the total population density N and the fraction of susceptible hosts x as

$$\frac{dN}{dt} = N\left[xb_S(N, x) + (1 - x)b_I(N, x) - \mu(N) - \alpha(1 - x)\right] \tag{2a}$$

$$\frac{dx}{dt} = (1 - x)\left[xb_S(N, x) + (1 - x)b_I(N, x) - \beta(\alpha)x + \alpha x\right]. \tag{2b}$$

Assume that, in the absence of pathogens, the host population settles at a nontrivial equilibrium, say N^*. In the deterministic setting, a pathogen strain with virulence α is able to invade a naive host population precisely when its basic reproduction ratio

$$\mathcal{R}_0(\alpha) = \frac{\beta(\alpha)}{\mu(N^*) + \alpha} \tag{3}$$

exceeds one. From now on we assume that $\mathcal{R}_0(\alpha) > 1$, i.e. we consider only strains that can invade a naive host population.

Suppose now that the pathogen is endemic and focus on the viability of the host population. According to (2), the fraction of susceptible hosts x changes faster than the total population density N whenever N is in a vicinity of zero. For N close to zero we can therefore assume that x attains a quasi-equilibrium x_0 implicitly defined by the equation

$$x_0 b_S(0, x_0) + (1 - x_0)b_I(0, x_0) - (\beta(\alpha) - \alpha)x_0 = 0 \tag{4a}$$

and approximate the changes in N with the equation

$$\frac{dN}{dt} = N\left[x_0 b_S(0, x_0) + (1 - x_0)b_I(0, x_0) - \mu(0) - \alpha(1 - x_0)\right]. \tag{4b}$$

The host population goes extinct if the expression in the brackets of (4b) is negative; using (4a), this is equivalent to

$$V(\alpha) := \beta(\alpha)x_0 - \mu(0) - \alpha \tag{5}$$

being negative (note that x_0 also depends on α).

Consider α as a bifurcation parameter for the dynamical system in (2). This system undergoes a transcritical bifurcation at $\alpha = \alpha_{\text{ext}}$ when $V(\alpha_{\text{ext}}) = 0$ holds together with

(4a) (provided that $V'(\alpha_{\mathrm{ext}}) \neq 0$). If this bifurcation is of the forward type (as it is in both models we study below; (Boldin (2006))), then it corresponds to the transition between host persistence and extinction. If extinction occurs, it occurs via a continuous decline of host population density N to zero. In the context of system (2), which assumes a closed population and frequency-dependent incidence, this bifurcation is of codimension 1. In the original model (1), however, x is not defined when $N = 0$ (but is defined in the limit $N \to 0$). If $V'(\alpha_{\mathrm{ext}}) < 0$, then extinction occurs when α increases beyond α_{ext}, whereas if the opposite holds, then extinction occurs as α decreases. Extinction may happen due to increasing or decreasing virulence depending on how strongly the transmission rate β increases with virulence and how x_0 changes with changing α.

Suppose now that we have a viable host-pathogen system. Can virulence evolve in such a way that the system is driven to extinction?

3 Adaptive dynamics of virulence with a continuous transition to extinction: a tale of two models

Assume that a strain α is resident in the population and that the system settles at the equilibrium $(\hat{N}, \hat{x})$ (note that $\hat{N}$ and $\hat{x}$ depend on α). Assuming that multiple infections cannot occur, the initial growth of a mutant strain with virulence α_{mut} is given by

$$\frac{dI_{\mathrm{mut}}}{dt} = \left[\beta(\alpha_{\mathrm{mut}})\hat{x} - \mu(\hat{N}) - \alpha_{\mathrm{mut}}\right]I_{\mathrm{mut}}$$

and therefore the mutant invades successfully if its long-term growth rate

$$r(\alpha_{\mathrm{mut}}, \alpha) = \beta(\alpha_{\mathrm{mut}})\hat{x} - \mu(\hat{N}) - \alpha_{\mathrm{mut}} \tag{6}$$

is positive. If mutations are of small effect ($|\alpha_{\mathrm{mut}} - \alpha|$ is small) and are infrequent such that the ecological and evolutionary time scales are separated, then virulence evolves towards higher or lower values depending on whether the selection gradient

$$D(\alpha) = \left.\frac{\partial r}{\partial \alpha_{\mathrm{mut}}}\right|_{\alpha_{\mathrm{mut}}=\alpha} = \beta'(\alpha)\hat{x} - 1 \tag{7}$$

is, respectively, positive or negative (Geritz et al. (1998)).

Let now α_{ext} be a bifurcation point given by $V(\alpha_{\mathrm{ext}}) = 0$. If the selection gradient

$$D(\alpha_{\mathrm{ext}}) = \beta'(\alpha_{\mathrm{ext}})x_0(\alpha_{\mathrm{ext}}) - 1 \tag{8}$$

is positive, then evolutionary suicide occurs at $\alpha = \alpha_{\mathrm{ext}}$ whenever traits $\alpha < \alpha_{\mathrm{ext}}$ are viable and traits $\alpha > \alpha_{\mathrm{ext}}$ are not viable. If $D(\alpha_{\mathrm{ext}})$ is negative, then evolutionary suicide occurs at $\alpha = \alpha_{\mathrm{ext}}$ whenever traits $\alpha > \alpha_{\mathrm{ext}}$ are viable and traits $\alpha < \alpha_{\mathrm{ext}}$ are not viable. In other words, evolutionary suicide occurs at $\alpha = \alpha_{\mathrm{ext}}$ if and only if $D(\alpha_{\mathrm{ext}})$ and $V'(\alpha_{\mathrm{ext}})$ have opposite signs. We have now arrived at the following

Theorem 1. *Let the dynamics of the host-pathogen system be described by the system of differential equations in (2) and let $x_0(\alpha)$ be a quasi-equilibrium corresponding to the extinction state $N = 0$, i.e. a solution of (4a). Let $V(\alpha)$ be as in (5) and let α_{ext} satisfy $V(\alpha_{\text{ext}}) = 0$. Furthermore, let the selection gradient in α_{ext}, $D(\alpha_{\text{ext}})$, be as in (8). If $x_0(\alpha_{\text{ext}})$ is a stable equilibrium of (2b) corresponding to the extinction state $N = 0$ then evolutionary suicide occurs at $\alpha = \alpha_{\text{ext}}$ if and only if*

$$\text{sign}(D(\alpha_{\text{ext}})) \neq \text{sign}(V'(\alpha_{\text{ext}})). \tag{9}$$

In agreement with Boots and Sasaki (2003) and Bernhauerová and Berec (2015), we demonstrate below that the adaptive dynamics of α can indeed make the system cross a bifurcation point α_{ext} given by $V(\alpha_{\text{ext}}) = 0$. By considering two special cases of (2) we show that evolutionary suicide can occur in two different ways, either by pathogen evolving towards higher virulence or (less intuitively) towards lower virulence, and explicitly demonstrate that evolutionary suicide occurs via a continuous decline of host population density towards zero.

Gyllenberg and co-workers proved that in the context of local bifurcations of the population dynamics (and with the evolving trait considered as the bifurcation parameter), a discontinuous transition to extinction is a necessary condition for evolutionary suicide to occur in a wide class of models under mild assumptions (Gyllenberg et al. (2002); Gyllenberg and Parvinen (2001)). One of these assumptions is that invasion fitness is well defined also in the extinction state of the population. This assumption holds in most models of ecology, but does not hold in the present model. When the pathogen has driven the host population extinct so that $S = N = 0$, the fraction of susceptible hosts, $x = S/N$, is undefined, and therefore the invasion fitness in (6) does not exist. The limit of x at the point of extinction (x_0 in (4)) however does exist, and determines the direction of evolution according to the selection gradient in (7) when $\alpha \to \alpha_{\text{ext}}$ in a viable system.

3.1 Model I

We first investigate a toy model in which the per capita birth rates of susceptible and infected hosts, b_S and b_I, respectively, depend only on the fraction of susceptible hosts x, i.e.

$$\frac{dN}{dt} = N\Big[xb_S(x) + (1-x)b_I(x) - \mu(N) - \alpha(1-x) \Big] \tag{10a}$$

$$\frac{dx}{dt} = (1-x)\Big[xb_S(x) + (1-x)b_I(x) - \beta(\alpha)x + \alpha x \Big]. \tag{10b}$$

The system in (10) is a generalization of the model considered in Berec and Maxin (2013). In Berec and Maxin (2013), the authors investigate an epidemiological model of a partially sterilizing, sexually transmitted disease in which they take into account the fact that in sexually transmitted diseases, host population birth rates and the rate of infection transmission are both mediated by the mating process. Assuming that $\sigma \in [0,1]$ is the

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probability of not becoming sterile upon infection and that both partners must be fertile to produce offspring, they arrive at

$$
\begin{aligned}
b_S(x) &= b[x + \sigma(1 - x)] \\
b_I(x) &= \sigma b_S(x)
\end{aligned}
\tag{11}
$$

for some positive constant b. In general, we expect b_S and b_I to be increasing functions of x as the number of fertile matings can decrease if the pathogen (partially) sterilizes the host.

3.1.1 Resident population dynamics

When the disease is not present in the population, the host population density changes according to the equation

$$
\frac{dN}{dt} = N\left[b_S(1) - \mu(N)\right].
$$

We assume that $b_S(1) > \mu(0)$ such that the trivial equilibrium $N = 0$ is unstable. When μ is an increasing function of the population density N, the condition $b_S(1) > \mu(0)$ guarantees the existence of a unique, globally stable positive equilibrium N^* whenever $\lim_{N \to \infty} \mu(N) > b_S(1)$. We assume that such an equilibrium exists and determine N^* as the solution of $\mu(N) = b_S(1)$. Since by assumption $\mathcal{R}_0 > 1$, the disease-free equilibrium $(N^*, 1)$ of (10) is unstable (see Appendix B for details).

The total population density, N, does not feature in (10b). Endemic equilibria of (10b) are found as solutions of $x b_S(x) + (1 - x) b_I(x) - \beta(\alpha) x + \alpha x = 0$ or, equivalently, as solutions of $G(x) = x$ where

$$
G(x) := \frac{b_I(x)}{b_I(x) - b_S(x) + \beta(\alpha) - \alpha}.
\tag{12}
$$

If $\mathcal{R}_0 > 1$ then

1. $-b_S(1) + \beta(\alpha) - \alpha > 0$ and since b_S is an increasing function of x it follows that $-b_S(x) + \beta(\alpha) - \alpha > 0$ for every $x \in [0, 1]$. If $b_I(x) \neq 0$ on $[0, 1]$ (as is the case with b_I in (11)) then $0 < G(x) < 1$ for every $x \in [0, 1]$.

2. $x \mapsto G(x)$ is an increasing function.

Hence, equation $G(x) = x$ has at least one solution in $(0, 1)$. The number of biologically meaningful equilibria depends on the precise form of the functions b_S and b_I. With b_S and b_I in (11), there is a unique positive equilibrium $\hat{x}$, which is globally stable (Berec and Maxin (2013)).

Let now $\hat{x}(\alpha)$ denote a stable equilibrium of (10b). Remember that $\hat{x}$ is independent of N. The asymptotic equation for the total host population density becomes

$$
\frac{dN}{dt} = N\left[\beta(\alpha)\hat{x}(\alpha) - \mu(N) - \alpha\right]
\tag{13}
$$

whereas V in (5) becomes

$$V(\alpha) = \beta(\alpha)\hat{x}(\alpha) - \mu(0) - \alpha. \tag{14}$$

If $V(\alpha) < 0$ then $N = 0$ is the only non-negative equilibrium of (13) and successful pathogen invasion drives the host-pathogen system to extinction. If, on the other hand, $V(\alpha) > 0$, the equilibrium $N = 0$ is unstable. Whenever $\lim_{N\to\infty}\mu(N) > \beta(\alpha)\hat{x}(\alpha) - \alpha$, there exists a unique positive equilibrium $\hat{N}$ which is globally stable.

The virulence of a strain that separates population persistence from population extinction, α_{ext}, therefore satisfies $V(\alpha_{\text{ext}}) = 0$. To demonstrate evolutionary suicide, we shall assume that $\mathcal{R}_0(\alpha_{\text{ext}}) > 1$.

3.1.2 Evolutionary suicide

For a resident strain α at the endemic equilibrium $(\hat{N}, \hat{x})$, the selection gradient is given by (7). Evolutionary suicide occurs at $\alpha = \alpha_{\text{ext}}$ when $D(\alpha_{\text{ext}})$ and $V'(\alpha_{\text{ext}})$ have opposite signs. Note that

$$V'(\alpha) = D(\alpha) + \beta(\alpha)\hat{x}'(\alpha). \tag{15}$$

The equilibrium value $\hat{x}$ satisfies $G(\hat{x}) = \hat{x}$ with G given in (12). To simplify the argument we consider birth rates of infected individuals of the form $b_I(x) = \sigma b_S(x)$ for some $\sigma \in [0, 1]$ (the birth rates used in numerical examples that follow have such a form; this assumption is however not necessary for evolutionary suicide). From implicit differentiation of $G(\hat{x}) - \hat{x} = 0$ we obtain

$$\hat{x}'(\alpha) = \frac{(1 - \beta'(\alpha))\hat{x}^2}{\sigma b_S(\hat{x}) - b_S'(\hat{x})(\sigma\hat{x}(1 - \hat{x}) + \hat{x}^2)}, \tag{16}$$

to be substituted in (15). Let us show that evolution to self-extinction can occur by adaptation towards either more or less virulent strains.

Evolutionary suicide caused by adaptation towards higher virulence. We can demonstrate evolutionary suicide at $\alpha = \alpha_{\text{ext}}$ assuming that $b_S'(\hat{x}(\alpha_{\text{ext}}))$ is sufficiently small for the denominator of $\hat{x}'(\alpha)$ in (16), evaluated at $\alpha = \alpha_{\text{ext}}$, to be positive. Consider first the degenerate situation where $D(\alpha_{\text{ext}}) = 0$, i.e., $\beta'(\alpha_{\text{ext}}) = \frac{1}{\hat{x}(\alpha_{\text{ext}})}$. In this degenerate case, by (15), the sign of $V'(\alpha_{\text{ext}})$ is given by the sign of $\hat{x}'(\alpha_{\text{ext}})$, which, according to (16), is negative since $1 - \beta'(\alpha_{\text{ext}}) = 1 - \frac{1}{\hat{x}(\alpha_{\text{ext}})} < 0$. By continuity, $V'(\alpha_{\text{ext}})$ remains negative also when $\beta'(\alpha_{\text{ext}})$ slightly exceeds $\frac{1}{\hat{x}(\alpha_{\text{ext}})}$, i.e. when $D(\alpha_{\text{ext}})$ is slightly positive. A suitable value of $\beta'(\alpha_{\text{ext}})$ therefore guarantees that strains in a vicinity of α_{ext} increase beyond the critical virulence α_{ext} into the extinction zone. When strains evolve higher virulence, infected hosts die faster, but also cause more secondary infections; in addition, changes in birth rates and in the density-dependent background mortality rate shift the equilibrium prevalence of the disease. If the infection prevalence increases (i.e., $\hat{x}$ decreases), then the average per capita death rate can increase (due to the disease-induced deaths) and the

average per capita birth rate can decrease (due to the lower birth rate of infected hosts as well as the dependence of the individuals' birth rates on the prevalence) to the extent that the population can no longer be sustained.

Evolutionary suicide caused by adaptation towards lower virulence. Suppose now that $\beta'(\alpha_{\text{ext}}) = 0$ so that $D(\alpha_{\text{ext}}) = -1$, i.e., the selection gradient is strongly negative. In this case, $V'(\alpha_{\text{ext}}) > 0$ (and evolutionary suicide happens) when $\beta(\alpha_{\text{ext}})\hat{x}'(\alpha_{\text{ext}}) > 1$ (cf. (15)). When substituting $\hat{x}'(\alpha_{\text{ext}})$ from (16) (with $\beta'(\alpha_{\text{ext}}) = 0$) into this last inequality, we distinguish two cases:

1. When $\sigma b_S(\hat{x}(\alpha_{\text{ext}})) < \beta(\alpha_{\text{ext}})\hat{x}^2(\alpha_{\text{ext}})$, then $\beta(\alpha_{\text{ext}})\hat{x}'(\alpha_{\text{ext}}) > 1$ holds if $b'_S(\hat{x}(\alpha_{\text{ext}})) = 0$. In this case, evolutionary suicide can occur without the infection prevalence affecting the per capita birth rates of the hosts. When the (locally constant) birth rate of infected individuals, σb_S, is sufficiently low, a constant transmission rate leads to evolutionary suicide at α_{ext}. By continuity, the same holds also if the transmission rate increases sufficiently slowly with virulence.

2. When $\sigma b_S(\hat{x}(\alpha_{\text{ext}})) > \beta(\alpha_{\text{ext}})\hat{x}^2(\alpha_{\text{ext}})$, then evolutionary suicide via decreasing virulence cannot occur with (locally) constant birth rates, but may still occur if the birth rates change with infection prevalence. For $\beta'(\alpha_{\text{ext}}) = 0$, $\beta(\alpha_{\text{ext}})\hat{x}'(\alpha_{\text{ext}}) > 1$ holds when the denominator of (16) is positive and sufficiently small, more precisely when

$$\frac{\sigma b_S(\hat{x}(\alpha_{\text{ext}})) - \beta(\alpha_{\text{ext}})\hat{x}^2(\alpha_{\text{ext}})}{\sigma \hat{x}(\alpha_{\text{ext}})(1 - \hat{x}(\alpha_{\text{ext}})) + \hat{x}^2(\alpha_{\text{ext}})}$$
$$< b'_S(\hat{x}(\alpha_{\text{ext}})) < \frac{\sigma b_S(\hat{x}(\alpha_{\text{ext}}))}{\sigma \hat{x}(\alpha_{\text{ext}})(1 - \hat{x}(\alpha_{\text{ext}})) + \hat{x}^2(\alpha_{\text{ext}})}.$$

Starting with a strain in a vicinity of α_{ext}, evolution decreases virulence beyond α_{ext}. As the rate of pathogen transmission does not decrease significantly by decreased virulence and infected individuals live longer, infection prevalence increases for constant or moderately prevalence-dependent birth rates (cf. (16)). If infected individuals either have sufficiently low birth rates, or the birth rates decrease quickly enough with increasing prevalence, evolution to self-extinction occurs.

3.1.3 Numerical examples

We demonstrate the two pathways to evolutionary suicide by two numerical examples. We take the birth rates b_S and b_I as given by (11) with $b = 2$ and $\sigma = 0.7$. We furthermore assume that the background mortality is of the form $\mu(N) = \mu_0 e^{0.01N}$ and the transmission-virulence trade-off is $\beta(\alpha) = \frac{10\alpha}{\beta_0\alpha+1}$ for some constants μ_0 and β_0.

Example 1. *Let $\beta_0 = 0.1$, $\mu_0 = 0.5$.*
In this case $\mathcal{R}_0(\alpha) > 1$ for $\alpha \in [0.23, 87.77]$. Starting with mild initial strains, evolution increases virulence past the critical point $\alpha_{\text{ext}} = 1.18$ (denoted by the red dot in the pairwise
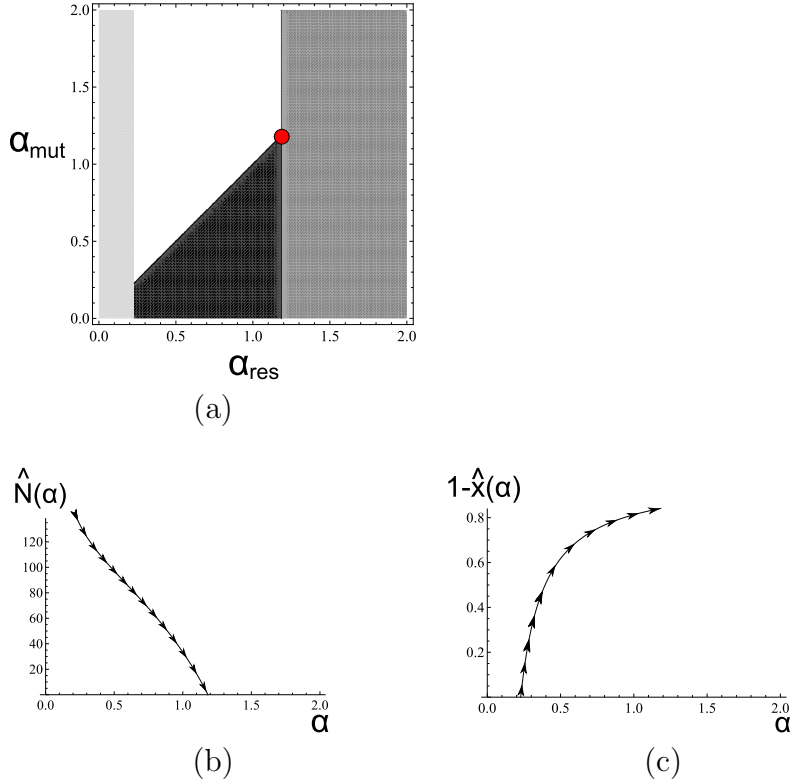
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Figure 1: Example 1: (a) Pairwise invasibility plot (PIP): white and black regions correspond to, respectively, positive and negative invasion fitness; in light grey region strains cannot invade a naive host population; in dark grey region, pathogens drive the host population to extinction. To increase visibility, we restrict the maximal virulence to 2. The red dot depicts the point of extinction, α_{ext}. (b) Graph of $\alpha \mapsto \hat{N}(\alpha)$. Arrows depict the direction of evolution. (c) Graph of $\alpha \mapsto 1 - \hat{x}(\alpha)$. Arrows depict the direction of evolution.

invasibility plot in Figure 1a), beyond which the pathogen drives its host (and itself) to extinction. As virulence increases towards the extinction point α_{ext}, the corresponding equilibrium values of the host population density, $\hat{N}(\alpha)$, decrease continuously to zero (cf. Figure 1b). With adaptation towards higher virulence the prevalence $1 - \hat{x}(\alpha)$ increases (cf. Figure 1c).

Example 2. *Let now $\beta_0 = 1$, $\mu_0 = 0.1$.*

Here, $\mathcal{R}_0(\alpha) > 1$ for $\alpha \in [0.29, 6.70]$. When starting with a highly virulent strain, evolution decreases virulence past the critical point $\alpha_{\text{ext}} = 6$ (depicted by the red dot in Figure 2a), beyond which the pathogen drives the host and itself to extinction. As infected hosts live longer when virulence decreases, the prevalence $1 - \hat{x}(\alpha)$ increases (cf. the right end of Figure 2c). Again, the host population density continuously declines to zero as virulence approaches the critical value α_{ext} (cf. the right end of Figure 2b).

Note however that, in this example, the host-pathogen system is protected from extinc-
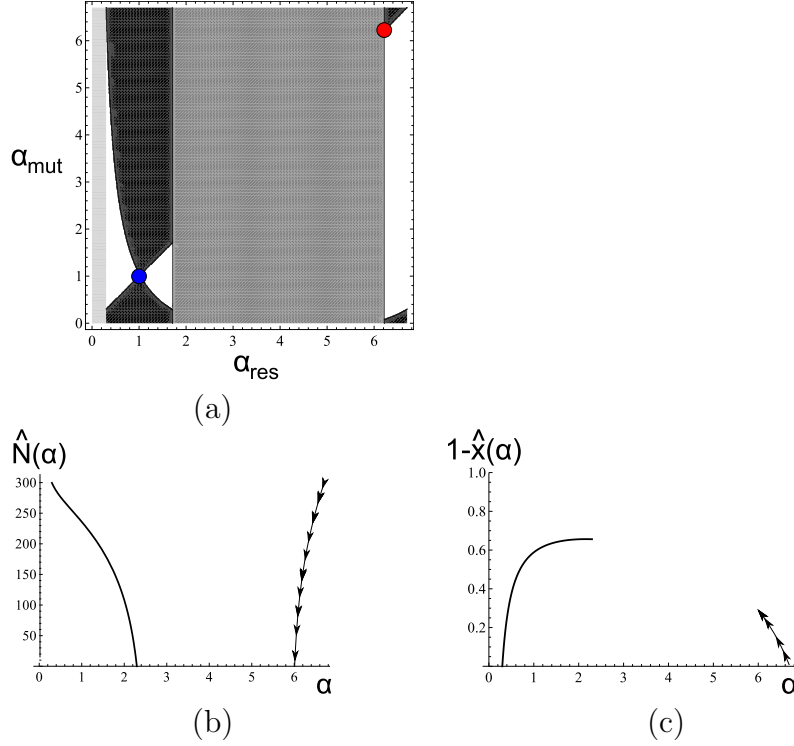
Figure 2: Example 2: (a) PIP: white and black regions correspond to, respectively, positive and negative invasion fitness; in light grey region strains cannot invade a naive host population; in dark grey region, the pathogen drives the host population to extinction. The red and the blue dot depict, respectively, the extinction point α_{ext} and the CSS virulence α_{CSS}. (b) Graph of $\alpha \mapsto \hat{N}(\alpha)$. Arrows depict the direction of evolution when initial virulence exceeds α_{ext}. (c) Graph of $\alpha \mapsto 1 - \hat{x}(\alpha)$. Arrows depict the direction of evolution when initial virulence exceeds α_{ext}.

tion when relatively mild strains are circulating in the population. When initial strains have low virulence, pathogens evolve to a CSS close to $\alpha = 1$ (depicted by the blue dot in Figure 2a).

3.2 Model II

We now look at a model where per capita birth rates of susceptible and infected hosts, b_S and b_I respectively, depend only on the total population density and consider the system

$$\frac{dN}{dt} = N\left[b_S(N)x + b_I(N)(1 - x) - \mu(N) - \alpha(1 - x)\right] \tag{17a}$$

$$\frac{dx}{dt} = (1 - x)\left[b_S(N)x + b_I(N)(1 - x) - \beta(\alpha)x + \alpha x\right]. \tag{17b}$$

We assume that b_S and b_I are decreasing functions of N such that $b_I(N) \leq b_S(N)$.

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3.2.1 Resident population dynamics

In the absence of the disease, equation

$$\frac{dN}{dt} = N\Big[b_S(N) - \mu(N)\Big]$$

describes the dynamics of host population density in time. We assume that $b_S(0) - \mu(0) > 0$ so that the trivial equilibrium $N = 0$ is unstable. Nontrivial equilibria are solutions of $b_S(N) - \mu(N) = 0$. If b_S and μ are such that a unique nontrivial solution, N^*, exists, then the population stabilizes at N^* in absence of the disease. We assume that this is indeed the case. Since by assumption $\mathcal{R}_0 > 1$, the disease-free equilibrium $(N^*, 1)$ is unstable (see Appendix C for details). In order to analyse the existence of endemic equilibria of (17) and their stability, we observe from (17) that nontrivial equilibrium values of N (if they exist) are solutions of

$$F(N) = R(N)\hat{x}(N) = 1 \tag{18}$$

where

$$R(N) = \frac{\beta(\alpha)}{\mu(N) + \alpha}, \tag{19a}$$

$$\hat{x}(N) = \frac{b_I(N)}{b_I(N) - b_S(N) + \beta(\alpha) - \alpha}. \tag{19b}$$

If $\hat{N}$ is a biologically meaningful solution of (18), the corresponding $\hat{x}$ is calculated from (19b). An endemic equilibrium $(\hat{N}, \hat{x})$ is therefore such that the expected number of secondary infections caused by one newly infected individual in the environment $(\hat{N}, \hat{x})$ in all of its infectious life is equal to one. We observe the following:

1. $N \mapsto R(N)$ is a non-increasing function of N with $R(N^*) = \mathcal{R}_0 > 1$.

2. $\hat{x}(N)$ is biologically meaningful ($0 \leq \hat{x}(N) \leq 1$) precisely when $f(N) := -b_S(N) + \beta(\alpha) - \alpha \geq 0$. Since f is an increasing function of N with $f(N^*) = (\mu(N^*) + \alpha)(\mathcal{R}_0 - 1) > 0$, the range of meaningful values of N is some interval $[N_0, N^*]$ (which may, or may not contain 0).

3. $N \mapsto \hat{x}(N)$ is a decreasing function of N in the region where $f(N) \geq 0$. Hence, F is a decreasing function of N in the region where $f(N) \geq 0$.

4. $F(N^*) = \frac{\mathcal{R}_0 b_I(N^*)}{b_I(N^*) + (\mu(N^*) + \alpha)(\mathcal{R}_0 - 1)} < 1$ since $b_I(N^*) \leq b_S(N^*) = \mu(N^*) < \mu(N^*) + \alpha$.

We distinguish two cases:

Case I. $f(0) = -b_S(0) + \beta(\alpha) - \alpha < 0$

There exists a unique positive value N_0 such that $f(N_0) = 0$ and we focus on the interval $[N_0, N^*]$. Note that $F(N_0) = R(N_0) > 1$ since $R(N)$ is decreasing in N and $R(N^*) = \mathcal{R}_0 > 1$. In this case, there exists a unique $\hat{N} \in (N_0, N^*)$ that solves $F(N) = 1$. The corresponding $\hat{x} = \hat{x}(\hat{N})$ is biologically meaningful, which gives a unique endemic equilibrium $(\hat{N}, \hat{x})$ of (17). The equilibrium $(\hat{N}, \hat{x})$ is locally stable (see Appendix C for details). The only other (meaningful) equilibria of (17) are $(0, 1)$ and $(N^*, 1)$, which are both unstable.

Case II. $f(0) = -b_S(0) + \beta(\alpha) - \alpha > 0$

The range of biologically meaningful values of N is $[0, N^*]$. We conclude:

1. if $F(0) > 1$ there exists a unique positive $\hat{N}$ that solves $F(N) = 1$. The corresponding $\hat{x} = \hat{x}(\hat{N})$ is biologically meaningful, which gives a unique endemic equilibrium $(\hat{N}, \hat{x})$ of (17). Again, this equilibrium is locally stable. In addition to the endemic equilibrium, there exists the steady state $(0, x_0)$ with

$$x_0 = \frac{b_I(0)}{b_I(0) - b_S(0) + \beta(\alpha) - \alpha}. \tag{20}$$

   The equilibrium $(0, x_0)$ is unstable (see Appendix C for details).

2. Whenever $F(0) < 1$, there is no positive solution of $F(N) = 1$. It is straightforward to check that in this case, the equilibrium $(0, x_0)$ with x_0 in (20) is locally stable (cf. Appendix C).

The only remaining equilibria of (17) are $(0, 1)$ and $(N^*, 1)$, which are both unstable.

It is worth pointing out that, when $\mu(0)$ increases, the value of $F(0)$ is pushed below one and the stable endemic equilibrium disappears. Hence, when background mortality rates are high enough, a successful invasion of the pathogen results in extinction of the whole system.

Suppose that a resident strain α settles at an endemic equilibrium $(\hat{N}, \hat{x})$ where $\hat{N}$ is the solution of (18) and the corresponding $\hat{x}$ is obtained from (19b). Inserting the thus obtained $\hat{x}$ in (7) yields the selection gradient for the current model. Note that, if in the course of pathogen evolution virulence α and transmission rate $\beta(\alpha)$ are such that the assumption of Case I holds, then host population densities remain bounded away from zero and evolutionary suicide is not possible. Evolution towards extinction is possible only when virulence and transmission rates are such that the condition of Case II is satisfied. Observe also that the unique positive equilibrium $(\hat{N}, \hat{x})$ depends continuously on the evolving parameter α. Evolutionary suicide, if it occurs, is therefore necessarily non-catastrophic.

3.2.2 Evolutionary suicide

We focus on virulence values α and transmission rates $\beta(\alpha)$ such that $\beta(\alpha) - \alpha > \max\{\mu(N^*), b_S(0)\}$. This guarantees that (i) $\mathcal{R}_0 > 1$ and (ii) the interval of meaningful population densities is $[0, N^*]$ (i.e. we consider Case II in which evolutionary suicide is possible).

   The preceding analysis reveals that the critical value of virulence α_{ext}, which separates population extinction from population persistence, satisfies $F(0)|_{\alpha=\alpha_{\text{ext}}} = 1$ (again, we assume that $\mathcal{R}_0(\alpha_{\text{ext}}) > 1$). Hence, evolutionary suicide occurs at $\alpha = \alpha_{\text{ext}}$ whenever

$$\text{sign } D(\alpha_{\text{ext}}) \neq \text{sign } \frac{d}{d\alpha} F(0)\Big|_{\alpha=\alpha_{\text{ext}}}. \tag{21}$$

Note that, with V defined in (5) and x_0 as in (20), we have

$$\text{sign } \frac{d}{d\alpha} F(0)\Big|_{\alpha=\alpha_{\text{ext}}} = \text{sign } V'(\alpha_{\text{ext}}),$$

and therefore the condition in (21) is equivalent to the condition for evolutionary suicide given in (9) .

   From implicit differentiation of (18) evaluated at $N = 0$, we obtain

$$b_I(0)\beta(\alpha_{\text{ext}})\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}}$$
$$= \beta'(\alpha_{\text{ext}})\Big[b_I(0) - (\mu(0) + \alpha_{\text{ext}})\Big] + \Big[(\mu(0) + \alpha_{\text{ext}}) - \frac{b_I(0)\beta(\alpha_{\text{ext}})}{\mu(0) + \alpha_{\text{ext}}}\Big] \tag{22}$$

and so the sign of $\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}}$ coincides with the sign of the right-hand side of (22). Let us show that evolution to self-extinction can occur by increasing as well as decreasing virulence.

Evolutionary suicide caused by adaptation towards higher virulence. When $\beta'(\alpha_{\text{ext}}) = \frac{1}{\hat{x}(0)} = \frac{\beta(\alpha_{\text{ext}})}{\mu(0)+\alpha_{\text{ext}}}$ (i.e. when $D(\alpha_{\text{ext}}) = 0$) equation (22) simplifies to

$$b_I(0)\beta(\alpha_{\text{ext}})\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}} = -(\mu(0) + \alpha_{\text{ext}})\Big[\frac{\beta(\alpha_{\text{ext}})}{\mu(0) + \alpha_{\text{ext}}} - 1\Big] < 0 \tag{23}$$

and so $\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}} < 0$. Hence, $\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}}$ is negative also when $\beta'(\alpha_{\text{ext}})$ is slightly above $\frac{\beta(\alpha_{\text{ext}})}{\mu(0)+\alpha_{\text{ext}}}$, i.e. when $D(\alpha_{\text{ext}})$ is slightly positive. Evolutionary suicide occurs at $\alpha = \alpha_{\text{ext}}$ such that evolution increases virulence beyond the point where the population is no longer viable.

Evolutionary suicide caused by adaptation towards lower virulence. We distinguish two cases.

1. If $b_I(0) > \mu(0) + \alpha_{\text{ext}}$ (i.e. if the birth rate of infected hosts is high enough so that even a fully infected host population is viable) then evolutionary suicide is not possible. In this case, $\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}} < 0$ whenever $\beta'(\alpha_{\text{ext}}) = \frac{1}{\hat{x}(0)}$ (see (23)) and therefore also whenever $\beta'(\alpha_{\text{ext}}) < \frac{1}{\hat{x}(0)}$ such that $D(\alpha_{\text{ext}}) < 0$ (see (22)).

14

2. If $b_I(0) < \mu(0) + \alpha_{\text{ext}}$ evolutionary suicide becomes possible if in addition $(\mu(0) + \alpha_{\text{ext}}) - \frac{b_I(0)\beta(\alpha_{\text{ext}})}{\mu(0)+\alpha_{\text{ext}}} > 0$. Indeed, $\frac{d}{d\alpha}F(0)|_{\alpha=\alpha_{\text{ext}}}$ is then positive for $\beta'(\alpha_{\text{ext}}) = 0$, which implies $D(\alpha_{\text{ext}}) < 0$. By continuity, the same holds also when $\beta'(\alpha_{\text{ext}})$ is slightly above zero.

When virulence decreases and transmission rates remain practically unchanged, a higher fraction of the population is infected. If the birth rate of infected hosts is sufficiently low, then the population can no longer persist and evolutionary suicide occurs.
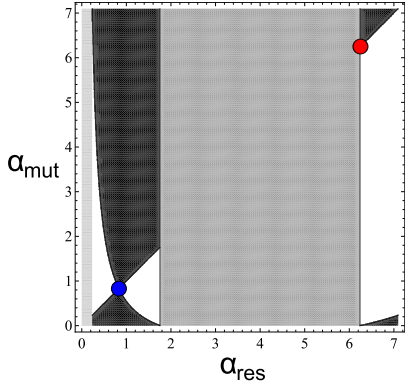
3.3 Numerical examples

In the examples that follow, we assume that $b_S = b\left(1 - \frac{N}{K}\right)$ with $b = 2$, $K = 1000$ and that $b_I = \sigma b_S$ with $\sigma = 0.5$. We furthermore assume the per capita background host mortality to be of the form $\mu(N) = 0.01(N + \mu_1)$ for some positive μ_1. Lastly, the trade-off between transmission and virulence is assumed to be $\beta(\alpha) = \frac{10\alpha}{1+\alpha}$.
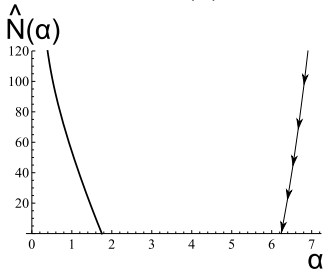
Example 3. *Let $\mu_1 = 1$.*

In this case, $\mathcal{R}_0(\alpha) > 1$ for $\alpha \in [0.24, 7.10]$. Pathogens evolve towards an intermediate level of virulence $\alpha_{\text{CSS}} = 0.84$ (depicted by the blue dot in Figure 3a) when initial strains are mild. When the initially introduced strain is highly virulent, however, evolution drives the pathogen towards lower virulence and past the critical point $\alpha_{\text{ext}} = 6.25$ (depicted by the red dot in Figure 3a) beyond which the host population, along with the pathogens, becomes extinct. As this happens, the host population density declines to zero continuously (cf. the right end of Figure 3b).
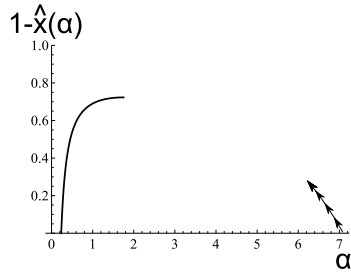
Example 4. *Let $\mu_1 = 80$.*

With this example, we demonstrate the devastating effect of increased background mortality. When the natural death rate of a host is low then mild initial strains evolve towards some intermediate level of virulence (cf. Figure 3a), keeping the host population and itself viable. When some factors unrelated to the disease (such as food availability or temperature) sufficiently increase the host's natural mortality rate, then even mild strains might drive the population towards extinction. As μ_1 increases, the CSS increases beyond α_{ext}. When relatively harmless initial strains evolve higher virulence they pass the critical value $\alpha_{\text{ext}} = 0.845$ (depicted by the red dot in Figure 4a) and the whole system becomes extinct (cf. Figure 4b). With adaptation towards higher virulence and therefore towards higher transmission, the prevalence $1 - \hat{x}$ increases (cf. Figure 4c).

Figure 3: Example 3: (a) PIP: white and black regions correspond to, respectively, positive and negative invasion fitness; in light grey region strains cannot invade a naive host population in dark grey region, the pathogen drives the host population to extinction. The red and the blue dot depict, respectively, the extinction point α_{ext} and the CSS α_{CSS}. (b) Graph of $\alpha \mapsto \hat{N}(\alpha)$. Arrows depict the direction of evolution when initial virulence exceeds α_{ext}. (c) Graph of $\alpha \mapsto 1 - \hat{x}(\alpha)$. Arrows depict the direction of evolution when initial virulence exceeds α_{ext}.
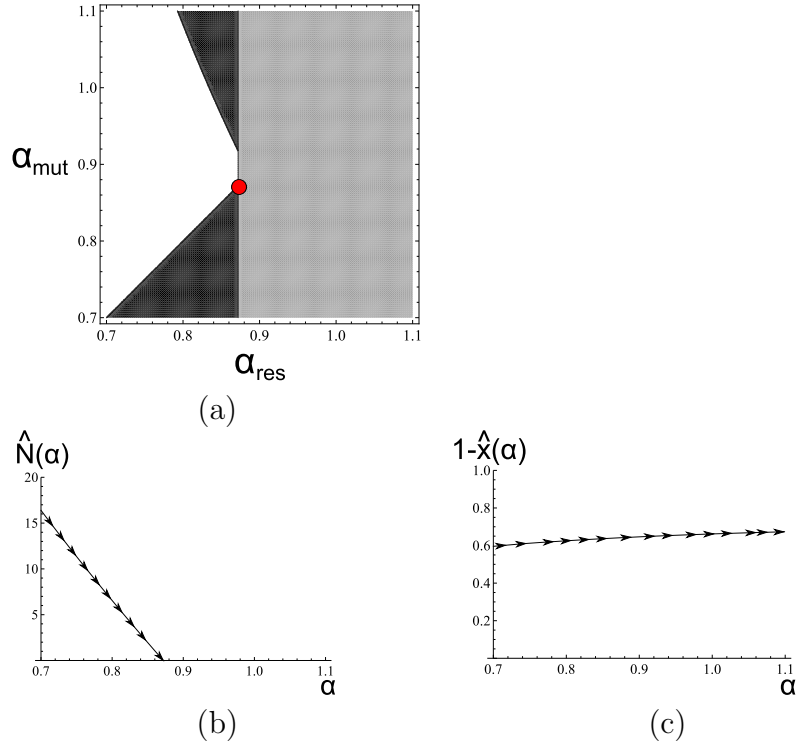
(a)

(b)

(c)

Figure 4: Example 4: (a) PIP: white and black regions correspond to, respectively, positive and negative invasion fitness; in grey region, the pathogen drives the host population to extinction. In this case $\mathcal{R}_0(\alpha) > 1$ for $\alpha \in [0.26, 6.94]$. For better viewing, we plot the PIP for $\alpha_{\mathrm{res}}, \alpha_{\mathrm{mut}} \in [0.7, 1.1]$. The red dot depicts the extinction point α_{ext}. (b) Graph of $\alpha \mapsto \hat{N}(\alpha)$. Arrows depict the direction of evolution. (c) Graph of $\alpha \mapsto 1 - \hat{x}(\alpha)$. Arrows depict the direction of evolution.

4 Discussion

Evolutionary suicide, i.e., evolution to self-extinction, is an intriguing phenomenon that has been found in a number of models of various ecological systems (Matsuda and Abrams (1994); Gyllenberg and Parvinen (2001); Gyllenberg et al. (2002); Parvinen (2007, 2010); Parvinen and Dieckmann (2013)). The notion itself is similar to the idea of the tragedy of the commons, originally put forward by Hardin (1968) (but see also Rankin et al. (2007)). In the context of pathogen evolution, Gandon and Day (2009) showed an example of evolutionary suicide via a catastrophic saddle-node bifurcation owing to an Allee effect in the host population dynamics. In all examples of evolution-driven extinctions cited above, evolutionary suicide happens via a discontinuous transition to extinction.

In this paper we consider a family of SI models for evolving pathogen virulence under frequency-dependent incidence. Here evolutionary suicide happens when the pathogen drives the entire host population extinct, including all infected hosts that carry the pathogen. Because the transmission rate of the pathogen is proportional to the frequency of susceptible hosts relative to the total host population size, the extinction state corresponds to a singularity in population dynamics and the invasion fitness is undefined in the extinction state. This violates the assumptions of Gyllenberg et al. (2002) and Gyllenberg and Parvinen (2001) and evolutionary suicide becomes possible also via a non-catastrophic transcritical bifurcation, i.e., such that the population density declines to zero continuously. We demonstrate this possibility with examples in Figures 1-4.

In absence of Allee effects, the assumption of a constant contact rate (i.e. frequency-dependent incidence) is crucial for evolutionary suicide. To see this, let $C(N)$ denote the contact rate as a function of population density. Generalizing the model in (2), the system

$$
\begin{aligned}
\frac{dN}{dt} &= N\left[xb_S(N,x) + (1-x)b_I(N,x) - \mu(N) - \alpha(1-x)\right] \\
\frac{dx}{dt} &= (1-x)\left[xb_S(N,x) + (1-x)b_I(N,x) - \beta(\alpha)xC(N) + \alpha x\right]
\end{aligned}
\tag{24}
$$

describes the dynamics of the host population density and the fraction of susceptible hosts. In frequency-dependent transmission we have $C(N) = 1$ for all population densities, whereas the classical mass-action assumption $C(N) = N$ yields the density-dependent incidence. Heesterbeek and Metz (1993) and Antonovics et al. (1995) use a Holling II - like argument to derive the rate of contacts $C(N)$ in a mechanistic manner. This leads to incidence functions that resemble density-dependent transmission at very low population densities and approximate frequency-dependent transmission when population density is sufficiently high. With mass-action description and the mechanistically derived contact rates in Heesterbeek and Metz (1993) and Antonovics et al. (1995) we have $C(0) = 0$. In such a case, the extinction state in (24) corresponds to the trivial equilibrium $(0,1)$ (cf. the only negative term in the right hand side of the second equation in (24) vanishes so that in equilibrum, x must go to 1 as N goes to zero), and $(0,1)$ is unstable in absence of Allee effects. Evolutionary suicide is therefore not possible in such models.

Frequency-dependent incidence is nevertheless a very popular model for sexually transmitted diseases, since due to the individuals actively searching for mates, the mating rate (which is the contact rate) can be constant for all but the lowest population densities. $C(N)$ saturates already at low densities also because of the long handling times, which include e.g. gestation and parental care (Antonovics et al. (1995)). Our model therefore properly describes the evolution of the pathogen until the host population density becomes very low. At small population sizes, the population dynamics is no longer deterministic, and there is a high risk of extinction due to demographic stochasticity (Boots and Sasaki (2003); Matsuda and Abrams (1994)). With a Holling II - like contact rate, therefore, evolutionary suicide may occur in the sense that the evolving pathogen drives the host below the minimum viable population size necessary for persistence in face of demographic stochasticity (Nunney and Campbell (1993)). This is similar to the runaway evolution found by Matsuda and Abrams (1994) and to the "gradual extinctions" examples of Webb (2003), but, importantly, in our models extinction occurs without the trait (here virulence) evolving unboundedly. Frequency-dependent incidence is also an accurate model for animals in herds; since the area the herd occupies shrinks in proportion to the decreasing number of individuals, the contact rate remains constant (de Jong et al. (1995)).

The majority of pathogens in nature utilize multiple transmission routes (e.g. direct host-to-host, vector-borne, environmental, vertical) (Antonovics et al. (1995); Ryder et al. (2007); Boldin and Kisdi (2012); Bernhauerová and Berec (2015)), thus making the traditional density-/frequency-dependent incidence dichotomy too simplistic. Instead, to realistically account for the richness in contacts leading to infection transmission, we might incorporate in our models a combination of density- and frequency-dependent transmission. As observed in Bernhauerová and Berec (2015), including vertical transmission to a model with frequency-dependent incidence does not remove the possibility of evolutionary suicide. Similarly, Ryder et al. (2007) reveals that evolution to self-extinction may be possible when density-dependent transmission is included into a model with frequency-dependent transmission (however, the scope for parasite-driven population extinctions narrows).

In our models, the host population goes extinct if the prevalence of the disease $(1 - \hat{x})$ is sufficiently high and the disease is harmful, in the sense that the birth rate of infected hosts is sufficiently low and/or their death rate is sufficiently high. Since a high death rate of the infecteds may lead to a low prevalence of the disease, evolutionary suicide may happen via two different routes, depending on how the disease-induced mortality (virulence) is linked to transmission and therefore to prevalence. We now discuss these two routes in turn.

Our general model in Appendix A demonstrates that if virulence is independent of transmission, the pathogen always evolves towards high transmission rates. This is in agreement with Boots and Sasaki (2003), but extended to the case where increasing transmission is not without any harm to the host: if the damage caused to the host by a more aggressively infectious pathogen is felt only in a reduced birth rate of the host, then the damage does not influence the evolution of transmission. From the pathogen's point

of view, producing new susceptibles via birth is akin to producing common goods for the pathogen. When shared with many individuals in a large population, the production of common goods provides no benefit to the individual and hence damaging the production does not influence individual fitness (Sigmund (2010)). As the pathogen evolves towards high transmission, the prevalence of the disease increases so that more hosts suffer from a low birth rate and from the (transmission-independent) disease-induced mortality, which may lead to the extinction of the host population.

Under the transmission-virulence trade-off, a similar route to evolutionary suicide exists. Evolution towards high transmission then amounts to evolution towards high virulence (as in Figures 1 and 4) and therefore to short-lived infections. If transmission increases fast enough, then prevalence still increases or at least remains sufficiently high, and the host population may go extinct if infected individuals have too low a birth rate and/or too high a mortality.

An alternative route to evolutionary suicide is when the pathogen evolves towards lower virulence (Figures 2 and 3). Infected individuals then live longer, and can infect more susceptibles provided that the transmission rate does not decrease too fast with decreasing virulence. As the prevalence of the disease increases, more hosts suffer from a low birth rate and from the disease-induced mortality, which may lead to the extinction of the host.

The second route to evolutionary suicide is particularly worrisome when considering pathogens jumping to new host species. A pathogen not yet adapted to its host may cause considerable harm, so that it has high initial virulence. As the pathogen evolves to reduce its virulence and hence to extend the infectious lifetime of its host, its prevalence increases and thereby it can drive its host to extinction.

It is well known that increasing background mortality triggers the evolution of higher transmission despite the cost of higher virulence (Lenski and May (1994)). Under frequency-dependent incidence, this effect can be rather dangerous, because increasing transmission can lead to evolutionary suicide and therefore to the loss of the host population. We illustrate this possibility with Model II, where initially mild pathogens evolve to an evolutionarily stable strain, but an increase of host background mortality selects for more transmissible strains until evolutionary suicide happens (Figures 3 and 4).

In adaptive dynamics, optimization models represent the special case that closest resembles the simple scenario of the 'survival of the fittest'. In particular, strategies cannot coexist when selection is optimizing (excluding the degenerate case of neutral coexistence), and adaptive dynamics leads to the maximization of a suitably chosen function of trait values, hence in this sense to the 'best' phenotype (Metz et al. (2008); Gyllenberg and Service (2011); Gyllenberg et al. (2011); Gyllenberg and Parvinen (2001)). Gyllenberg and Parvinen (2001) proved that in a wide class of optimization models, evolutionary suicide cannot occur via the typical route of a saddle-node bifurcation of population dynamics. Recently, Parvinen and Dieckmann (2013) showed by way of examples that evolutionary suicide is possible also in optimization models, via global bifurcations; a similar model was analyzed earlier by Webb (2003). The model of Boots and Sasaki (2003) is an optimization model predicting evolutionary suicide. In our extension of

this model, selection is generally frequency-dependent, but in some special cases, it is optimizing. The latter is the case if, in equation (1), the background mortality rate does not depend on population density (or, in the general model (25), the background mortality rate and the virulence do not depend on the environmental feedback variables) and the host population is regulated only via the birth rates, so that the invasion fitness of a mutant is a monotonic function of the single environmental feedback variable x (or $\langle x \rangle$), which implies optimization (Metz et al. (2008)). Whether or not selection is optimizing makes no qualitative difference for evolutionary suicide in these models. Note that this is possible because frequency-dependent incidence violates the assumptions of Gyllenberg and Parvinen (2001).

In the examples presented in this paper, evolutionary suicide occurs with evolving monomorphic pathogen populations. However, our models in general include more than one environmental feedback variable, thus allowing for coexistence of pathogen strains; this is true also for models including multiple transmission routes (see e.g. Boldin and Kisdi (2012); Bernhauerová and Berec (2015)). Evolutionary suicide may therefore be possible also via polymorphic evolution, with multiple coexisting strains driving the host-pathogen system to extinction. Evolutionary suicide in polymorphic populations has earlier been observed by Ferriere and Legendre (2013) in a model of cooperation (cf. Figure 7 in their paper). It remains to be seen whether such evolution-driven extinctions occur in host-pathogen systems with coexisting pathogen strains.

A Appendix: General model

Here we consider a rather general family of SI models given by

$$
\begin{aligned}
\frac{dS}{dt} &= b_S(\tilde{\mathbf{E}}(S,I,z),t)S + b_I(\tilde{\mathbf{E}}(S,I,z),z,t)I - \mu(\tilde{\mathbf{E}}(S,I,z),t)S - \beta(z)\frac{SI}{N} \\
\frac{dI}{dt} &= \beta(z)\frac{SI}{N} - \mu(\tilde{\mathbf{E}}(S,I,z),t)I - \alpha(\tilde{\mathbf{E}}(S,I,z),z,t)I.
\end{aligned}
\tag{25}
$$

As in the main text, S and I are the density of susceptible and infected hosts, respectively, and $N = S + I$ is the total host population density. z is a trait that characterizes the infecting strain of the pathogen (e.g. its intra-host proliferation rate, see e.g. Boldin and Diekmann (2008)). For the population dynamics of a given strain in (25), z is the parameter of interest for the bifurcation through which extinction happens. For the adaptive dynamics, z is the evolving trait. We assume that z determines the transmission rate $\beta(z)$ and also influences other demographic parameters (see below). In the models considered in the main text, we assumed that α, the virulence, is a pathogen-specific constant (i.e., independent of $\tilde{\mathbf{E}}$ and time) and took $z = \alpha$.

The vector $\tilde{\mathbf{E}}$ contains environmental feedback variables, such as the densities of available resources, which depend on the number of hosts who exploit these resources. Susceptible and infected hosts may exploit the resources differently (for example, infected hosts may be less efficient foragers), and the exploitation of infected hosts may depend on the trait value z of the infecting strain (for example, the more the strain damages the hosts, the less efficiently they forage), so that $\tilde{\mathbf{E}}$ depends on S, I and z. The per capita birth rates of susceptibles and infecteds, b_S and b_I, respectively, depend on the environmental feedback variables and, in the case of b_I, also on the infecting strain; with this latter assumption, we allow for a partially sterilizing pathogen whose degree of sterilization depends on its trait value z. Similarly, the background mortality rate (μ) and the virulence (α) depend on the environmental feedback variables, and, in the case of α, on the infecting strain. Finally, all birth and death rates may depend explicitly on time, i.e., they may be affected by external factors.

This model subsumes a wide variety of ecological assumptions (how the demographic rates depend on population density via resources etc.) and also a variety of possible effects of the pathogen on its host's demography, but retains the crucial assumption of frequency-dependent pathogen transmission. The model of Boots and Sasaki (2003) is a special case of (25) with $b_S(\tilde{\mathbf{E}}(S, I, z), t) = b - h(S + I)$, $\mu(\tilde{\mathbf{E}}(S, I, z), t) = u$, $\alpha(\tilde{\mathbf{E}}(S, I, z), z, t) = \bar{\alpha}$ (where b, h, u and $\bar{\alpha}$ are positive numbers), and either $b_I(\tilde{\mathbf{E}}(S, I, z), z, t) = 0$ (the disease is fully sterilizing) or $b_I(\tilde{\mathbf{E}}(S, I, z), z, t) = b - h(S + I)$ (the infected hosts have the same birth rate as the susceptibles).

As in the main text, we rewrite the system in terms of the total population density N and the fraction of susceptible hosts $x = \frac{S}{N}$ as

$$
\begin{aligned}
\frac{dN}{dt} &= N\left[xb_S(\mathbf{E}, t) + (1-x)b_I(\mathbf{E}, z, t) - \mu(\mathbf{E}, t) - (1-x)\alpha(\mathbf{E}, z, t)\right] \\
\frac{dx}{dt} &= (1-x)\left[xb_S(\mathbf{E}, t) + (1-x)b_I(\mathbf{E}, z, t) - x\beta(z) + x\alpha(\mathbf{E}, z, t)\right]
\end{aligned}
\tag{26}
$$

where $\mathbf{E} = \mathbf{E}(N, x, z) = \tilde{\mathbf{E}}(xN, (1-x)N, z)$. The invasion fitness of a mutant strain z_{mut} is given by

$$
\rho(z_{\mathrm{mut}}, z) = \beta(z_{\mathrm{mut}})\langle x \rangle - \langle \mu(\mathbf{E}(N, x, z), t) \rangle - \langle \alpha(\mathbf{E}(N, x, z), z_{\mathrm{mut}}, t) \rangle
\tag{27}
$$

where the angle brackets $\langle \cdot \rangle$ denote the time-averages on the ecological timescale of equation (26) (Metz et al. (1992)); we assume that these expectations exist. If the resident dynamics in (26) are autonomous (i.e., if the birth and death rates do not depend explicitly on time) and the system attains an equilibrium, then the time-averages reduce to the values at the resident equilibrium. In this case, the environmental feedback variables that determine the invasion fitness of a given mutant are the fraction of susceptibles, x, and the elements of $\mathbf{E}$ at the resident equilibrium.

The adaptive dynamics of the pathogen trait z is governed by the selection gradient

$$
\begin{aligned}
D(z) &= [\partial\rho(z_{\mathrm{mut}}, z)/\partial z_{\mathrm{mut}}]_{z_{\mathrm{mut}}=z} \\
&= \beta'(z)\langle x \rangle - \left\langle \left.\frac{\partial\alpha(\mathbf{E}(N, x, z), z_{\mathrm{mut}}, t)}{\partial z_{\mathrm{mut}}}\right|_{z_{\mathrm{mut}}=z} \right\rangle.
\end{aligned}
\tag{28}
$$

Following Boots and Sasaki (2003), assume first that the disease-induced death rate is independent of the strain infecting the host, i.e., that $\alpha(\mathbf{E}(N, x, z), z_{\mathrm{mut}})$ does not depend on z_{mut} (but it may still depend on z via the environmental feedbacks). In other words, different strains z_{mut} of the pathogen differ in their transmission rate $\beta(z_{\mathrm{mut}})$ and may also differ in their effect on the birth rate of an infected host, $b_I(\mathbf{E}(N, x, z), z_{\mathrm{mut}}, t)$ so that a strain with a higher transmission rate may be more damaging to host fecundity. With this assumption, the selection gradient reduces to $D(z) = \beta'(z)\langle x \rangle$, which has the same sign as $\beta'(z)$. The pathogen therefore evolves to maximize its transmission rate. Assume further that the transmission rate can increase without bound, and $\beta(z) \to \infty$ as $z \to z_0$. Let the initial strain be such that the solution of $\frac{dz}{dt} = \beta'(z)$ tends to z_0 (if the function $z \mapsto \beta(z)$ does not have finite local maxima, then this is true for any initial value z). In this case, z evolves towards z_0.

If a strain z is viable, i.e., if in its resident population the density of infected hosts, I, is bounded and also bounded away from zero, then $\langle \frac{1}{I}\frac{dI}{dt} \rangle = 0$ must hold (cf. Metz et al. (1992)). By the second equation of (25), this is equivalent to

$$\beta(z)\langle x \rangle = \langle \mu(\mathbf{E}(N, x, z), t) + \alpha(\mathbf{E}(N, x, z), z, t) \rangle. \tag{29}$$

Since μ and α are bounded, we have $\langle x \rangle \to 0$ as $z \to z_0$; a very highly transmissible disease infects all hosts. The dynamics of the total population density then converges to the orbit of

$$\frac{dN}{dt} = \left[b_I(\mathbf{E}(N, 0, z_0), z_0, t) - \mu(\mathbf{E}(N, 0, z_0), t) - \alpha(\mathbf{E}(N, 0, z_0), z_0, t) \right] N. \tag{30}$$

If (30) has no other attractor than the trivial equilibrium $N = 0$, then the entire host population goes extinct. In absence of Allee-effects, the birth and death rates are monotonic functions of the elements of $\mathbf{E}$, which, in turn, are monotonic in N. In this case, the trivial equilibrium is the only attractor of (30) if

$$\langle b_I(\mathbf{E}(0, 0, z_0), z_0, t) - \mu(\mathbf{E}(0, 0, z_0), t) - \alpha(\mathbf{E}(0, 0, z_0), z_0, t) \rangle < 0. \tag{31}$$

As z evolves towards z_0, the entire host population goes extinct when (31) holds. The evolution of the pathogen thus results in its own extinction, i.e., in evolutionary suicide. In absence of Allee-effects, evolutionary suicide occurs as the host population density declines to zero continuously during the course of evolution. In autonomous systems, this happens via a local non-catastrophic bifurcation of population density.

In this Appendix, we assumed that the transmission rate can evolve to arbitrarily high values. In reality, the transmission rate is bounded by the rate of contacts between host individuals, and increasing the transmission rate may be possible only at the cost of increasing virulence (Alizon et al. (2009)). This model nevertheless shows, along the lines of Boots and Sasaki (2003) but in a much more general model, that with a sufficiently high contact rate and for some trade-off functions linking transmission and virulence, evolutionary suicide must be possible. In the main text of this article, we show that evolutionary suicide does happen through a non-catastrophic bifurcation also in models with bounded transmission traded off with virulence.

B Appendix: (In)stability of the disease-free equilibrium of Model I

The aim of this Appendix is to verify that the disease-free equilibrium of (10) is unstable whenever $\mathcal{R}_0 > 1$ and locally stable when $\mathcal{R}_0$ is below 1. The linearization of (10) around $(N^*, 1)$ gives

$$\begin{bmatrix} -N^*\mu'(N^*) & * \\ 0 & -b_S(1) + \beta(\alpha) - \alpha \end{bmatrix}.$$

The upper left element of the Jacobian at $(N^*, 1)$ is negative. Since $-b_S(1) + \beta(\alpha) - \alpha > 0 \iff \mathcal{R}_0(\alpha) > 1$, the disease-free equilibrium $(N^*, 1)$ is unstable when $\mathcal{R}_0(\alpha) > 1$ and locally stable whenever $\mathcal{R}_0(\alpha) < 1$.

C Appendix: Local stability of equilibria of Model II

In this Appendix we discuss stability of equilibria of Model II.

The linearization of (17) takes the form

$J(N, x)$

$$= \begin{bmatrix} (b_S(N)x + b_I(N)(1-x) - \mu(N) - \alpha(1-x)) & N(b_S(N) - b_I(N) + \alpha) \\ +N(b'_S(N)x + b'_I(N)(1-x) - \mu'(N)) & \\ (1-x)(b'_S(N) + b'_I(N)(1-x)) & (1-x)(b_S(N) - b_I(N) - \beta(\alpha) + \alpha) \\ & -(b_S(N)x + b_I(N)(1-x) - \beta(\alpha)x + \alpha x) \end{bmatrix}.$$

The assumption $b_S(0) > \mu(0)$ implies that the equilibrium $(0, 1)$ is unstable. If we further assume that $\mathcal{R}_0 > 1$, the disease-free steady state $(N^*, 1)$ is unstable.

If an endemic equilibium $(\hat{N}, \hat{x})$ exists then the Jacobian evaluated in $(\hat{N}, \hat{x})$ has the form

$$J((\hat{N}, \hat{x})) = \begin{bmatrix} \hat{N}(b'_S(\hat{N})\hat{x} + b'_I(\hat{N})(1-\hat{x}) - \mu'(\hat{N})) & \hat{N}(b_S(\hat{N}) - b_I(\hat{N}) + \alpha) \\ (1-\hat{x})(b'_S(\hat{N})\hat{x} + b'_I(\hat{N})(1-\hat{x})) & (1-\hat{x})(b_S(\hat{N}) - b_I(\hat{N}) - \beta(\alpha) + \alpha) \end{bmatrix}$$

which has the sign structure

$$\begin{bmatrix} - & + \\ - & - \end{bmatrix},$$

implying that $(\hat{N}, \hat{x})$ is locally stable whenever it exists.

If the assumption of Case I holds, then there are no other equilibria of (17). The same conclusions holds in Case II (i). When the assumption of Case II (ii) holds, there is no endemic equilibrium of (17). There exists however an equilibrium $(0, x_0)$ with $0 < x_0 < 1$. We have

$$J((0, x_0)) = \begin{bmatrix} \beta(\alpha)x_0 - \mu(0) - \alpha & 0 \\ * & (1-x_0)(b_S(0) - b_I(0) - \beta(\alpha) + \alpha) \end{bmatrix}.$$

Since both diagonal elements are negative, the equilibrium $(0, x_0)$ is locally stable.

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