On the evolutionary dynamics of pathogens with direct and environmental transmission

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Abstract

A number of ecologically and economically important pathogens exhibit a complex transmission dynamics that involves distinct transmission modes. In this paper, we study the evolutionary dynamics of pathogens for which transmission includes direct host-to-host as well as indirect environmental transmission. Different routes of infection spread require specific adaptations of the parasite, which may result in conflicting selection pressures. Using the framework of Adaptive dynamics, we investigate how these conflicting selection pressures are resolved in the course of evolution and determine the conditions for evolutionary diversification of pathogen strains. We show that evolutionary branching and subsequent evolution of specialist strains occurs in wide parameter regions but evolutionary bi-stability and evolution of generalist pathogens are possible as well. Our analysis reveals that the relative contributions of direct and environmental transmission, as well as the underlying ecological dynamics, play a crucial role in shaping the course of pathogen evolution. Our findings may explain the coexistence of high and low virulence strains observed in several pathogenic organisms utilising different transmision modes (e.g. influenza viruses) and highlight the importance of considering ecological dynamics in virulence management.

Keywords: Adaptive dynamics, evolutionary branching, bi-stability, direct transmission, environmental transmission, virulence

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Introduction

Studies of the evolutionary dynamics of pathogen life-history traits tend to focus on evolutionary changes in virulence in pathogens transmitted exclusively upon a contact of an infectious host with a susceptible individual (but see e.g. Ewald (1983) and Dieckmann et al. (2002)). Virulence, defined here as the host's infection induced mortality, has been shown empirically to be positively correlated with parasite's transmissibility (for a recent review, see Alizon et al. (2009)). Directly transmitted pathogens thus face a delicate task of balancing the gains of increased transmission to new hosts and the losses suffered due to shortening the expected life-span of their host. Simple models of virulence evolution predict that such trade-offs between transmissibility and virulence result in evolution of a single strain of intermediate virulence, but more realistic ecological settings, host-heterogeneity and multiple infections predict more complex evolutionary dynamics, including evolutionary branching and evolutionary bi-stability (Nowak and May (1994); Mosquera and Adler (1998); Pfennig (2001); Dieckmann et al. (2002); Gandon (2004); Green et al. (2006); Boldin and Diekmann (2008); Alizon (2008); Svennungsen and Kisdi (2009)).

In many ecologically and economically important pathogens, transmission occurs via two, or even more, distinct transmission routes. Human pathogens such as HIV, HTLV-I, hepatitis B and C, for example, can all be transmitted vertically (i.e. from mother to offspring) as well as directly (Bittencourt (1998); Dunn et al. (1994); Thaler et al. (1991); Lipsitch et al. (1996)). Mixed vertical and direct transmission has also been documented for many plant pathogen species (van den Bosch et al. (2010)). Some other pathogenic organisms produce free parasites that survive for non-negligible periods of time outside their hosts, which enables the parasite to be transmitted indirectly via an outside environment, such as contaminated soil or household surfaces. Influenza viruses, smallpox and bacterial genera *Bacillus* and *Clostridium* are all examples of such pathogens. Within one infected host, HIV can be transmitted directly from one target cell to another, as well as environmentally via free virions (Deeks (2011); Sigal et al. (2011)). Nosocomial pathogens, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) and Vancomycin-resistant *Enterococcus* (VRE), utilise a combination of direct host-to-host, environmental and vector-borne transmission.

Alternative modes of transmission require specific adaptations of the parasite and a mutation that enhances transmission via one of the routes may hamper the spread of infection in other ways. For a pathogen with mixed direct and environmental transmission, for example, increased longevity of spores in an outside environment requires the parasite to develop a persistent coat, which may, in turn, decrease the chances of infection upon a host-to-host contact (Caraco and Wang (2008)). Multiple transmission modes may thus generate conflicting selection pressures and trade-offs between the different transmission modes. How are these conflicting selection pressures resolved in the course of adaptation? In this paper, we investigate this question for pathogens utilising direct and environmental transmission.

Studies of strictly environmentally transmitted pathogens have traditionally focused

on the relation between longevity of free parasites and virulence, investigating the so called 'curse of the pharaoh' hypothesis that parasites with long-lived spores necessarily evolve high virulence (Bonhoeffer et al. (1996); Gandon (1998); Caraco and Wang (2008)). One of the conclusions of the studies of Bonhoeffer et al. (1996), Gandon (1998) and Caraco and Wang (2008) is that a single strain emerges as the outcome of adaptation. In fact, all three models are optimization models and thus unable to explain coexistence of pathogen strains.

To our knowledge, the studies of Day (2002) and Roche et al. (2011) are the only two studies that investigate the evolution of pathogens with mixed direct and environmental transmission. In the model of Day (2002), pathogens can be transmitted via three routes: (i) directly, (ii) indirectly through release of free pathogens while the host is alive or (iii) indirectly through release upon the host's death. Despite the seemingly large scope for coexistence, the model includes an assumption that severly limits the possible evolutionary outcomes: the rate at which a susceptible host encounters free propagules in the environment is proportional to the environmental pathogen load (in other words, mass action incidence is assumed). The upshot is that the model is an optimization model and hence also unable to explain evolutionary coexistence od strains. The assumption of mass action incidence is replaced by a saturating incidence in the recent study by Roche et al. (2011). While coexistence of pathogen strains is observed in a population dynamical context, the emergence of pathogen diversity via evolutionary branching is not found. Instead, the authors observe either a single evolutionary winner or evolutionary bi-stability (i.e., two continuously stable strategies, separated by an evolutionary repeller), where the outcome of pathogen adaptation depends on the virulence of the initial strain. Overall, thus, no theoretical studies can account for evolutionary diversification and coexistence in infectious diseases that are transmitted both directly and environmentally.

The aim of the current paper is to present a rather general model that incorporates direct host-to-host transmission as well as indirect environmental spread of an infection. We investigate how the relative strengths of the two transmission modes shape the course of pathogen adaptation and determine the conditions under which we expect diversification and subsequent coexistence of pathogen strains on the evolutionary time-scale. We show that, by creating two environmental feedback variables, the two transmission modes can induce the evolution of strain diversity, but only under certain conditions. In other cases, evolutionary bi-stability or evolution of a single generalist strain are observed. Our analysis reveals that ecological dynamics plays an important role in shaping the course of pathogen evolution.

The model

We base our model on a simple SIR framework (Diekmann and Heesterbeek (2000)) and assume that the total population comprises of susceptible (S), infected (and infectious; I) and recovered hosts (R) and denote by $N = S + I + R$ the total host population size. In addition, we include an environmental reservoir and denote by P the number of free

parasites.

We assume that susceptible individuals are born at a constant rate b and die at per capita rate d. A susceptible host can become infected either through a contact with an infected individual (i.e., by direct transmission), or environmentally, by coming into contact with a free parasite. The rate at which a susceptible host makes contact with another host depends on the size of the total population, N, and is denoted by $f(N)$. If a contact is made with an infected host (which occurs with probability $\frac{I}{N}$), infection is transmitted with probability β. The rate at which a susceptible host comes into contact with pathogen spores in the environment depends on the total environmental load, P, and is denoted by $g(P)$. Upon contact with a free parasite, a susceptible becomes infected with probability γ. We assume that multiple infections do not occur, neither via the environment, nor via host-to-host transmission. The detrimental effect of infection is modeled as an increase in host's death rate and is denoted by α. In epidemiological literature, the infection induced death rate is commonly reffered to as virulence. Infected hosts recover at a rate ρ and are immune upon recovery. An infected host produces free pathogens at a rate θ. There is no pathogen release upon the host's death. Finally, we assume that free parasites in the environment die at a rate σ.

The above assumptions can be translated into the following system of differential equations:

$$\begin{aligned}
\frac{dS}{dt} &= b - \beta f(N)\frac{SI}{N} - \gamma g(P)S - dS \\
\frac{dI}{dt} &= \beta f(N)\frac{SI}{N} + \gamma g(P)S - (d+\alpha+\rho)I \\
\frac{dN}{dt} &= b - dN - \alpha I \\
\frac{dP}{dt} &= \theta I - \sigma P,
\end{aligned} \tag{1}$$

Note that the depletion of free pathogens due to infection is neglected in (1). This omission does not bring visible changes to the results, it does, however, greatly simplify the analysis (see Dwyer (1994)). Note also that, if $\rho = 0$, we are dealing with a chronic infection and the model is an extension of a simple SI model. For readers' convenience we summarize the parameters and their meaning in Table 1.

Our aim in this paper is to study the evolution of a phenotypic characteristic of the pathogen. The evolving trait will be denoted by x and can, as is done traditionally, represent virulence, but can also refer to some other pathogen characteristic, such as its within-host reproduction rate. When considering epidemiological and evolutionary dynamics of pathogenic organisms, pathogen life-history characteristics can not be viewed as independent traits but are instead tied to each other via trade-offs. Trade-offs between pathogen transmissibility and virulence have been extensively studied for directly transmitted pathogens (for a recent review, see Alizon et al. (2009)). With an additional transmission route, the pathogen is faced with further restrictions. For example, survival outside the host requires the pathogens to evolve resistant spores, which, in turn, decreases the probability of infection upon a contact with a susceptible host (Caraco and

Notation	Meaning
S	abundance of susceptible hosts
I	abundance of infected hosts
N	total host population size
P	abundance of free pathogens
b	population birth rate
d	per capita natural death rate
α	per capita disease induced death rate (virulence)
ρ	per capita recovery rate
θ	rate at which free parasites are produced by infected hosts
σ	rate of decay of free pathogens
β	probability of infection on contact infected - susceptible
γ	probability of infection on contact susceptible - free parasite
x	evolving trait
$f(N)$	per capita rate of contacts among hosts
$g(P)$	rate of contact between a susceptible and free parasites

Table 1: Notation

Wang (2008)). To keep our model as general as possible, the parameters $\alpha, \beta, \theta, \sigma, \gamma$ and ρ will all be allowed to depend on the evolving trait x. In a special, and most frequently studied case, the evolving trait is virulence (i.e. $x = \alpha$) and the remaining traits are tied to α. Note that, for a specific host-pathogen system, only some of the trade-offs $\alpha(x), \beta(x), \theta(x), \sigma(x), \gamma(x)$ and $\rho(x)$ may be 'active' while other parameters may simply be considered as constants. The host's demographic parameters, b and d, will be assumed to be fixed on the time-scale of pathogen evolution.

In addition to the flexibility in trade-offs between various pathogen traits, the model is rather general when it comes to incidence functions f and g. Classical examples of contact rates between hosts include the mass action incidence, $f(N) = N$, and the standard incidence, $f(N) = 1$. Examples of contact rates between hosts and free-living parasites include the mass action incidence, $g(P) = P$, and the family of functions given by $g(P) = \frac{\phi P}{P+\kappa}$. The latter can be obtained mechanistically from an individual-based model that describes how a susceptible moves about the contaminated area (see Breban et al. (2010) for details). Our goal in the current paper is to perform a detailed analysis for the special case of (1) where host-to-host contacts are made according to the mass action principle, i.e., $f(N) = N$. Incidence g, on the other hand, will be kept general. Biologically meaningful incidence functions g are non-decreasing functions that saturate for large values of pathogen load P. To simplify the analysis, we assume that g is a twice differentiable, positive and concave function. Since the contact rate g is zero whenever

free pathogens are absent, we can write

$$g(P) = P\ G(P)$$

for some function G for which $G'(P) \leq 0$.

With mass action incidence $f(N) = N$, the equations for $\frac{dS}{dt}$, $\frac{dI}{dt}$ and $\frac{dP}{dt}$ in eq. (1) form a closed system, which means we can omit the equation for $\frac{dN}{dt}$ and focus on the system

$$\begin{aligned}
\frac{dS}{dt} &= b - \beta SI - \gamma SPG(P) - dS \\
\frac{dI}{dt} &= \beta SI + \gamma SPG(P) - (d + \rho + \alpha)I \\
\frac{dP}{dt} &= \theta I - \sigma P.
\end{aligned} \tag{2}$$

We refer the interested reader to the companion paper by Kisdi and Boldin (in preparation), in which we present some results on the general model (1).

In order to study the evolutionary dynamics by means of Adaptive dynamics, we must understand the epidemiological dynamics with a single pathogen strain. In Supplementary material A we show that a unique positive equilibrium of (2) exists whenever the basic reproduction ratio (Diekmann and Heesterbeek (2000))

$$R_0 = \frac{b}{d}\Big(\frac{\beta}{d + \alpha + \rho} + \frac{\gamma\theta G(0)}{\sigma(d + \alpha + \rho)}\Big) \tag{3}$$

exceeds one. Whenever it exists, the endemic equilibrium is stable, while the infection-free equilibrium is unstable whenever $R_0 > 1$. If R_0 is below one, the only equilbrium is the disease-free equilibrium, which is then stable.

It is important to note that, despite the potentially large number of trade-offs that come into play, all the trade-offs enter the basic reproduction number via two composite functions, D and E, given by

$$D = \frac{\beta}{d + \alpha + \rho}, \tag{4a}$$

$$E = \frac{\gamma\theta}{\sigma(d + \alpha + \rho)}. \tag{4b}$$

The functions D and E indicate, respectively, the strength of direct and environmental transmission (Roche et al. (2011)). This observation will prove useful in the evolutionary analysis that follows.

Evolutionary invasion analysis

Suppose that a resident strain x_r is in a population dynamical equilibrium. A slightly different mutant strain x_m may affect any of the parameters (except for the host's demographic parameters, b and d, which are assumed to be fixed). We denote by α_m the

virulence of the mutant strain and use a similar short-hand notation to denote the remaining parameter values of the mutant.

The simplest way to determine the invasion fitness of a mutant is to look at its growth on a generation basis. The per generation growth factor of a mutant trait x_m in a monomorphic resident community with trait x_r, $R_0(x_r, x_m)$, is given by

$$R_0(x_r, x_m) = \hat{S}\Big[\frac{\beta_m}{\alpha_m + \rho_m + d} + \frac{\theta_m \gamma_m}{\sigma_m(\alpha_m + \rho_m + d)} \frac{g(\hat{P})}{\hat{P}}\Big] = \hat{S}\Big[D(\alpha_m) + E(\alpha_m) G(\hat{P})\Big], \quad (5)$$

where $\hat{S}$ and $\hat{P}$ denote, respectively, the equilibrium value of susceptible host population and the equilibrium abundance of free pathogens, as they are determined by the resident strain x_r. Note that D and E in the invasion fitness in (5) depend only on the mutant's trait value and not on the resident.

Evolutionarily singular strategies (Geritz et al. (1998)) are solutions of the equation

$$D'(x) + E'(x) G(\hat{P}(x)) = 0. \quad (6)$$

Since $G(\hat{P})$ is positive, it is clear that singular strategies can not be found in parameter regions in which increasing (or decreasing) trait value simultaneously improves both transmission routes.

Let now x^* denote a singular trait value. Evolutionary stability of a singularity is determined by the sign of

$$\frac{\partial^2 R_0}{\partial x_m^2}\Big|_{x_m = x_r = x^*} = S(x^*)\Big[D''(x^*) + E''(x^*) G(\hat{P}(x^*))\Big]. \quad (7)$$

If the expression in (7) is negative, the singularity is uninvadable, while a positive value implies that the singularity can be invaded by nearby strategies (Geritz et al. (1998)). Using (6), we can rewrite (7) as

$$\frac{\partial^2 R_0}{\partial x_m^2}\Big|_{x_m = x_r = x^*} = S(x^*) E'(x^*) \Big(\frac{D'(x)}{E'(x)}\Big)'\Big|_{x = x^*}. \quad (8)$$

Hence, if $E'(x^*) > 0$ (i.e., if an increase in the trait value will enhance environmental transmission) the singular strategy is invadable precisely when

$$\Big(\frac{D'(x)}{E'(x)}\Big)'\Big|_{x = x^*} > 0. \quad (9)$$

Since in that case $D'(x^*) < 0$, we can say that the singularity is invadable when the loss in direct transmission is overcompensated by the gain in environmental transmission. If that is not the case, the singularity is uninvadable. Similarly, if $E'(x^*) < 0$, the singularity is invadable precisely when the loss in environmental transmission (that occurs when the trait is increased) is overcompensated by the gain in direct transmission.

To determine which of the singular strategies act as (local) evolutionary attractors, we look at the second derivative

$$\frac{\partial^2 R_0}{\partial x_m^2}\Big|_{x_m=x_r=x^*} + \frac{\partial^2 R_0}{\partial x_r \partial x_m}\Big|_{x_m=x_r=x^*}. \tag{10}$$

If (10) is negative, the singularity is convergence stable (i.e. a local attractor for evolutionary dynamics) while a positive value implies that the singularity is a local evolutionary repeller (Geritz et al. (1998)).

Evolutionary branching points, a source for evolutionary diversification of an initially monomorphic pathogen population, are singular points that are both convergence stable and invadable, and can occur only when the mixed second derivative

$$\mathcal{M} := \frac{\partial^2 R_0}{\partial x_r \partial x_m}\Big|_{x_m=x_r=x^*} = \hat{S}(x^*)E'(x^*)G'(\hat{P}(x^*))\hat{P}'(x^*) \tag{11}$$

is negative. Note that the singularity condition in (6) and $\mathcal{M}$ depend only on the first derivatives, while the invadability condition in (7) contains the second derivatives of D and E. By varying the convexities of the trade-offs at the singularity, without changing the values and the slopes of the trade-offs in the singular point, we can thus change the invadability of the singularity while keeping its position fixed (Bowers et al. (2005); Kisdi (2006)). In particular, we can devise trade-off functions that yield evolutionary branching points provided that $\mathcal{M} < 0$ in the singularity (for applications of this technique, called critical function analysis, to virulence evolution see the studies of Svennungsen and Kisdi (2009) and Boldin et al. (2009)).

With these preliminaries we can now investigate how the incidence function g and the trade-offs affect the possibility of evolutionary branching.

I. Mass action incidence for environmental transmission.

If $g(P) = P$, we recover the model of Day (2002). Invasion fitness takes the form

$$R_0(x_r, x_m) = \hat{S}\Big[D(x_m) + E(x_m)\Big].$$

In this case, there is but one environmental feedback variable ($\hat{S}$), evolution acts as optimization and coexistence is not possible, regardless of the shape of trade-offs. Since $R_0(x, x) = 1$, we can write

$$R_0(x_r, x_m) = \frac{D(x_m) + E(x_m)}{D(x_r) + E(x_r)},$$

from which it is clear that a mutant invades successfully precisely when it increases the total transmission success. Hence, the optimal strain is the one that (locally) maximizes $D + E$.

II. A concave incidence for environmental transmission.

Let now g be an arbitrary concave function (i.e. $g''(P) < 0$). Differentiation of the equilibrium equations of (2) (see (1) in Supplementary material A) and evaluation in a singularity yields

$$S'(D + EG(P)) + SEG'(P)P' = 0 \tag{12a}$$

$$(b - dS)E' = dS'E + \gamma P' + \gamma' P. \tag{12b}$$

If the probability of infection upon contact with a spore is independent of the evolving trait, i.e. $\gamma' = 0$, then expressing P' from (12b) and rewriting (12a) in the form $S' = -S^2 EG'(P)P'$ yields

$$\mathcal{M} = SE'G'(P)P' = \frac{S}{b - dS} P'^2 G'(P)(\gamma - dE^2 S^2 G'(P)).$$

Since $G'(P) \leq 0$, $\mathcal{M}$ is always negative. That is, branching is always possible whenever infectivity of a spore does not depend on the evolving trait (cf. Figure 1). Let us now suppose that γ is negatively correlated with the evolving trait, i.e. $\gamma' < 0$. This is meaningful to expect when, for example, the evolving trait is virulence or the within-host replication rate of the pathogen (Caraco and Wang (2008)). If $P' < 0$ in the singularity, then $\mathcal{M}$ is always negative. If, however, $P'(x^*) > 0$, then M is negative only when

$$\gamma' > \frac{P'}{P} \left(dE^2 S^2 G'(P) - \gamma \right) \tag{13}$$

i.e., if γ does not decrease too steeply in the singular point. If γ is positively related to the evolving trait then $\mathcal{M}$ is always negative whenever $P' > 0$ in the singularity. If $P'(x^*) > 0$ then $\mathcal{M}$ is negative only when the reversed inequality in (13) holds (i.e. when γ does not increase too steeply). We conclude that $\mathcal{M}$ is negative and thus evolutionary branching is possible at least in the situations where γ is weakly dependent on the evolving trait.

Classification of evolutionary scenarios

We have already observed that evolutionarily singular strategies can only lie inbetween the local maxima of D and E. Let us suppose for simplicity that both $D(x)$ and $E(x)$ have a unique maximum (if that is not the case, we may expect the possibilities described below inbetween any two consecutive local maxima of D and E). In view of the number of singular traits and their invadability, we can then classify the evolutionary scenarios as follows:

(i) **A single continuously stable strategy (CSS).** In such a case, the evolutionary winner is a generalist strain that prudently utilizes both transmission routes, possibly to a different extent. But is this generalist strain more virulent than the evolutionary winner in the case of pure host-to-host transmission? To answer this question,

we observe that, for a strictly directly transmitted pathogen, the invasion fitness (denoted by R_d) has the form

$$R_d(x_r, x_m) = \hat{S}_d \; D(x_m),$$

where $\hat{S}_d$ stands for the equilibrium abundance of susceptibles set by the resident strain in the context of a direct-transmission-only model (this model can be obtained from (2) by setting either $\theta = 0$ or $\gamma = 0$). Let x_d^* be the evolutionary winner in the pure host-to-host transmission model. Then $D'(x_d^*) = 0$. If an increase of trait value enhances environmental transmission (i.e. $E'(x_d^*) > 0$), then evolution in the case of mixed transmisson will proceed past the point that maximizes D. On the other hand, if $E'(x_d^*) < 0$ then evolution in the case of mixed transmission will favour lower trait values. Since E involves various trade-offs pertaining to pathogen's environmental transmission, one cannot make general conclusions as to whether mixed transmission leads to, for example, more virulent strains than direct transmission. Conclusions can only be drawn on a case to case basis where empirical studies can tell us something about the nature of the trade-offs for a specific host-pathogen system.

(ii) **A unique branching point.** If the loss (gain) in direct transmission is overcompensated by the gain (loss) in environmental transmission, then the singularity is invadable (cf. eq. (9)). When directional evolution drives the trait towards the singularity, the pathogen population becomes dimorphic in a vicinity of the singularity and the two morphs begin to specialize on different transmission modes. To investigate what happens with the pathogen population after branching, we proceed by studying the invasion fitness with a dimorphic resident population (see below).

(iii) **Evolutionary bi-stability (two continuously stable strategies, separated by a repeller).** In such a case, one of the two continuously stable strategies is predominantly transmitted directly, while the second transmits mostly via the environment. The outcome of pathogen adaptation depends on the trait of the initial strain and it is the evolutionary repeller that separates the domains of attraction. Since both attracting singular strategies are uninvadable, any dimorphisms in a vicinity of convergence stable strategies (if they exist at all) will be of a passing nature and evolution eventually ends in either a predominatly directly transmitted infection or in an infection largely transmitted via the environment.

(iv) **One continuously stable strategy, one branching point and an evolutionary repeller inbetween**. Again, the outcome of evolution depends on the initial strain: either a generalist strain evolves (note that this generalist strain may be biased towards one of the two transmission routes), or we have (at least initially) diversification and specialization to different transmission modes. The evolutionary repeller separates the domains of attraction.

(v) **Two branching points separated by a repeller**. Evolutionary branching is in this case initiated nearby any of the two convergence stable strategies. After

branching, the two strains begin to specialize on the different transmission routes. To see what happens with the pathogen population in the long run, we proceed by studying the invasion fitness with a dimorphic resident population (see below).

Examples of the adaptive dynamics of virulence

In this section we demonstrate the above evolutionary scenarios by focusing on a special, and most frequently studied case, in which the evolving trait is virulence (i.e. the disease induced death rate), $x = \alpha$.

The outcome of strain adaptation in a specific host-pathogen system will depend on the relative strengths of direct and environmental transmission. Given a large number of trade-offs in our model, there are several ways in which changes in the intensities of environmental and direct transmission can come about. For example, environmental transmission can be enhanced by increasing the rate at which the pathogens are released into the environment (i.e. by increasing θ) or by developing more persistent spores that survive longer outside the host (i.e. by decreasing σ). To illustrate the above evolutionary scenarios we present a series of numerical examples in which the strength of environmental transmission is varied by changing spore longevity. In particular, we assume that

$$\sigma(\alpha) = e^{-u\alpha} + v \tag{14}$$

for some positive constants u and v. In this way, the spores of avirulent strains are expected to survive $\frac{1}{1+v}$ units of time outside the host, while longevity can increase to at most $\frac{1}{v}$ when virulence increases towards infinity. The parameter u determines how quickly longevity can be increased by increasing virulence.

As suggested by Ewald (1994) and also more recently by Day (2002), the maximum of E is likely to be obtained for higher virulence values than the maximum of D since direct transmission requires infected hosts to be active whereas environmental transmission only requires hosts to transmit into an environmental pool contacted by susceptible hosts. In our numerical examples, we achieve this by tuning the parameter values. We furthermore assume that the incidence takes the form $g(P) = \frac{P}{P+1}$ (cf. Breban et al. (2010)). Figure 1 shows a series of pairwise invasability plots (Figures (b)-(f)) for different values of u in (14). When u is low (meaning that spore longevity is gained slowly by increasing virulence), we observe two continuously stable strategies, separated by an evolutionary repeller. In this case, the maxima of D and E are obtained for very different virulence levels and pathogen strains have to 'choose' between specialising on direct or indirect transmission. Which of the two will actually evolve depends on the virulence of the initial strain. When u is increased, and the peaks of D and E move closer to one another (cf. Figure 4), the upper of the two CSS (which corresponds to the strain that specializes on environmental transmission) becomes a branching point. When u is increased further, we observe a small parameter region in which both of the convergence stable singularities are invadable. By increasing u further, we observe another bifurcation in which the lower of the two singularities disappears. At first, we have a unique branching point but increasing

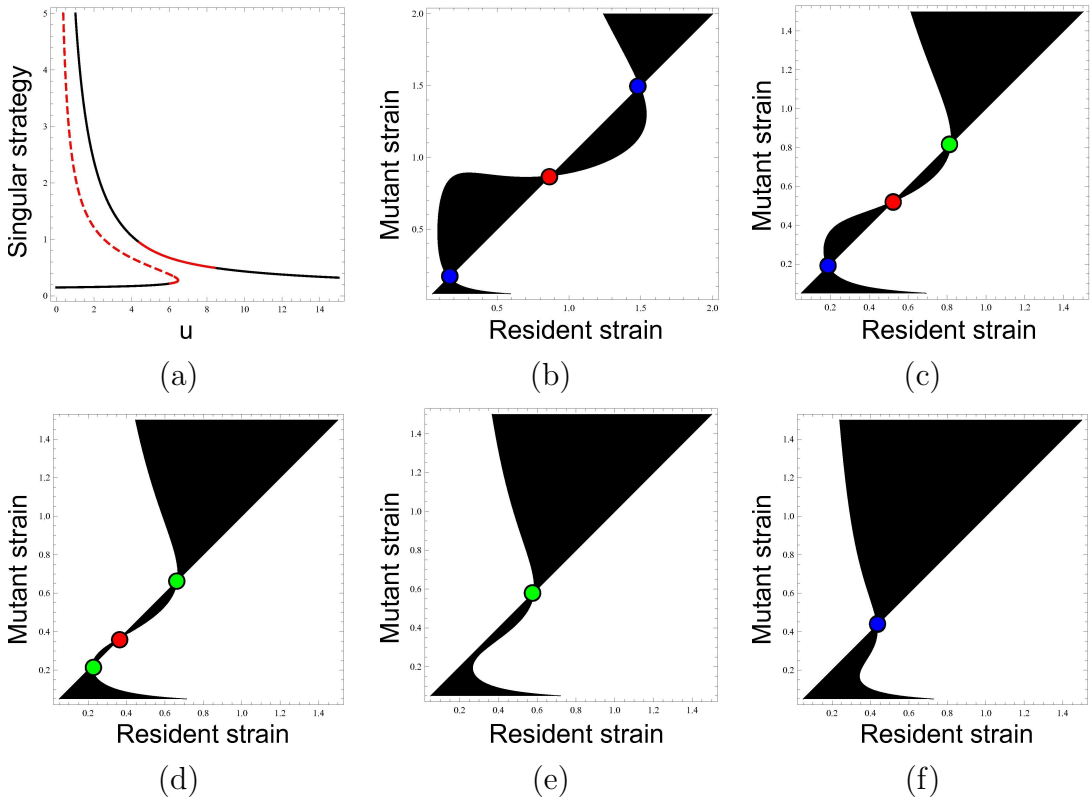
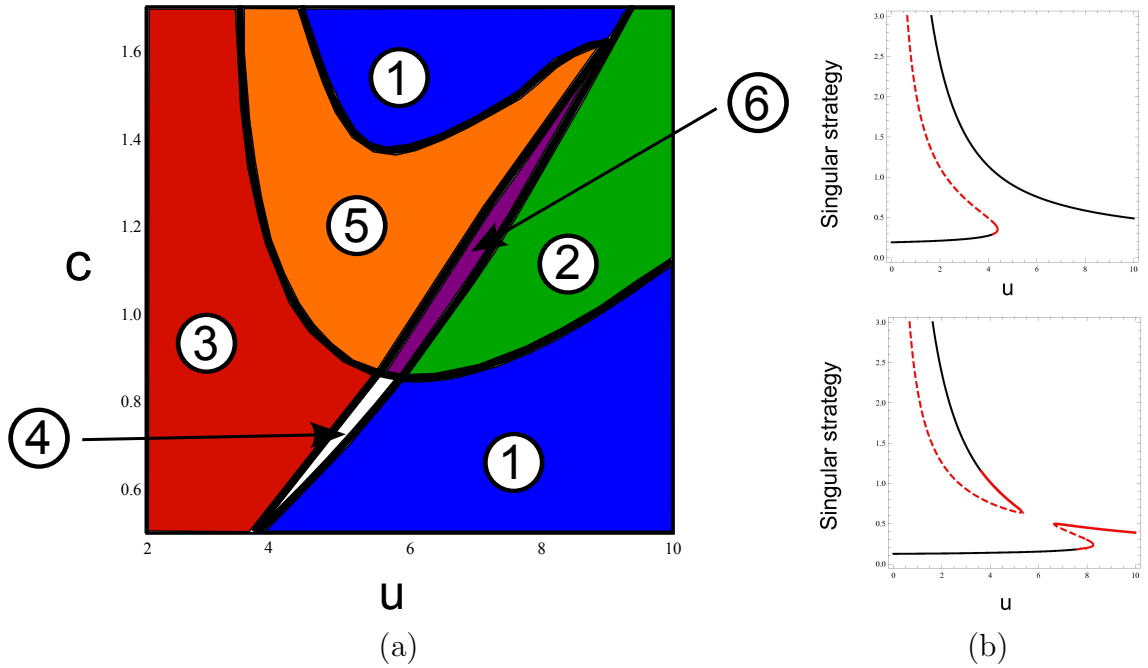


Figure 1: Parameter values and trade-off functions: $b = 1$, $\gamma = 0.35$, $\rho = 0$, $d = 0.2$, $\beta(\alpha) = \frac{\alpha}{\alpha+0.1}$, $\theta(\alpha) = \frac{\alpha}{\alpha+1}$ and $v = 0.02$. (a) Bifurcation plot: singular strategies as a function of u in (14). Black depicts continuously stable singularities, full red lines depict evolutionary branching points and dashed red curves represent evolutionary repellers. The remaining figures show pairwise invasibility plots with (b) $u = 3$, (c) $u = 5$, (d) $u = 6.1$, (e) $u = 7$ and (f) $u = 10$. In all the PIPs, blue circles depict continuously stable strategies (CSS), red circles show evolutionary repellers and green circles represent branching points.

u even further will cause the singularity to become a CSS. The figure showing the number of evolutionarily stable strategies along with their types is shown in a bifurcation diagram in Figure 1a, where black curves depict continuously stable singularities, full red lines represent evolutionary branching points and evolutionary repellers are depicted by dashed red curves.

Thus far we have investigated the evolutionary scenarios by varying only the strength of environmental transmission. To see how the outcome of strain adaptation, and in particular, the scope for evolutionary branching, changes when both transmission intensities are varied, we present in Figure 2a another bifurcation diagram. As in the previous example, we vary the strength of environmental transmission by changing u in (14). The



(a) (b)

Figure 2: (a) Bifurcation diagram: the number and type of singular strategies, depending on c in (15) and u in (14). Region 1 (in blue) depicts parameter regions in which a single CSS is found. In region 2 (in green), we have a single branching point. In regions 3-6, we have three singular strategies: in region 3 (in red) we have two CSSs, separated by a repeller. In region 4 (in white), the lower singularity is a branching point, the upper is a CSS. In region 5 (in orange), the upper singularity is a branching point, the lower is a CSS. In region 6 (in purple), both outer singularities are branching points. (b) Two bifurcation diagrams showing the value and the type of the singularity as a function of u: $c = 0.6$ in top and $c = 1.4$ in bottom figure. For the interpretation of curve types and another bifurcation diagram with $c = 1$, see Figure 1a.

strength of direct transmission is controled by varying parameter c in transmissibility β,

$$\beta(\alpha) = \frac{c\alpha}{c\alpha + 0.1}. \tag{15}$$

Figure 2a reveals that evolutionary branching is common in the context of our model. Indeed, regions 2, 4, 5 and 6, in which branching is observed, represent substantial portions of parameter space.

Dimorphic evolutionary dynamics

We now return to the general case in which the evolving trait is an arbitrary phenotypic characteristic of the parasite and focus on a situation where an initially monomorphic pathogen population turns dimorphic in a vicinity of a branching point. What can we say

about the subsequent adaptive dynamics? Will evolution lead the two morphs towards a dimorphic singular point? If a dimorphic singularity exists, how do the trait values of the strains that form a dimorphic singularity change when the relative strength of environmental (or direct) transmission is varied?

To gather more information about the evolution in dimorphic populations, we write the invasion fitness (again measured on a generation basis) in a dimorphic resident community with traits x_1 and x_2, $R_0(x_1, x_2, x_m)$. We have

$$R_0(x_1, x_2, x_m) = \tilde{S}\Big[D(x_m) + E(x_m)G(\tilde{P})\Big], \tag{16}$$

where $\tilde{S}$ and $\tilde{P}$ denote, respectively, the equilibrium values of susceptibles and free parasites in a dimorphic resident community with strains x_1 and x_2. We first observe that *any* two coexisting strains x_1 and x_2 satisfy the condition

$$\tilde{S}\Big[D(x_1) + E(x_1)G(\tilde{P})\Big] = \tilde{S}\Big[D(x_2) + E(x_2)G(\tilde{P})\Big] = 1.$$

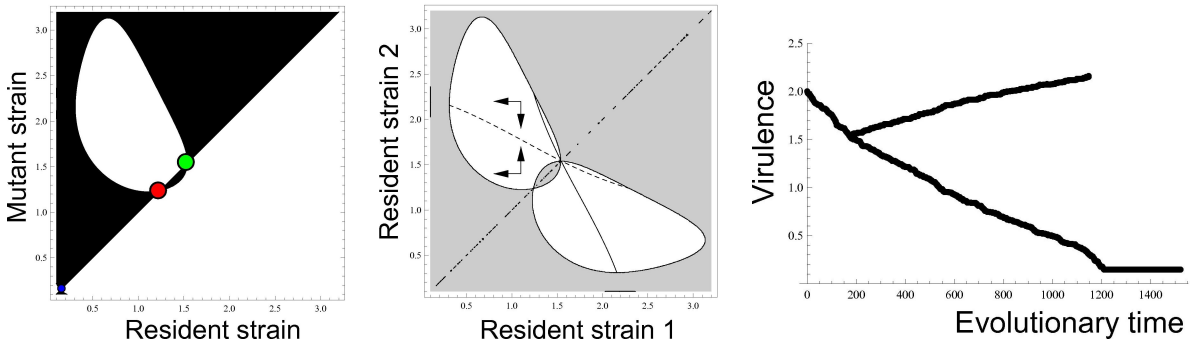
Hence, the straight line connecting the points $(E(x_1), D(x_1))$ and $(E(x_2), D(x_2))$ has slope $-G(\tilde{P}(x_1, x_2))$. If a coalition (x_1, x_2) is to be a dimorphic singularity, then in addition

$$\tilde{S}(D'(x_1) + E'(x_1)G(\tilde{P})) = 0 \tag{17a}$$

$$\tilde{S}(D'(x_2) + E'(x_2)G(\tilde{P})) = 0 \tag{17b}$$

has to hold. Since (17) implies that $\frac{D'(x_1)}{E'(x_1)} = \frac{D'(x_2)}{E'(x_2)} = -G(\tilde{P}(x_1, x_2))$, we can conclude that strains x_1 and x_2 form a dimorphic singularity precisely when the straight line connecting the points $(E(x_1), D(x_1))$ and $(E(x_2), D(x_2))$ is tangent to the parametrically given curve $(E(x), D(x))$ (see also Svennungsen and Kisdi (2009)). Thus, a simple graphical consideration of the parametric curve $(E(x), D(x))$ can give us candidates for dimorphic singularities. It remains to be seen whether such coalitions lie in the coexistence region. Note also that this graphical method gives us a dimorphic singularity in terms of $(E(x_1), D(x_1))$ and $(E(x_2), D(x_2))$, i.e. in terms of the strengths of environmental and direct transmission of the two strains. To obtain the singular coalition (x_1, x_2), we need to find the values x_1 and x_2 at which the precise values of D and E are reached.

As we demonstrate by way of an example in Figure 3, dimorphic singular strategies need not exist. In this particular example, evolutionary invasion analysis predicts a CSS and a branching point, separated by a repeller. If evolution drives virulence towards the branching point, the pathogen population splits into two morphs that initially undergo disruptive selection. However, dimorphic evolution ultimately drives the two strains towards the extinction boundary where one of the two strains goes extinct. After extinction, the pathogen evolves towards the CSS. Hence, even though the pairwise invasibility plot shows branching nearby the singular strategy that excels in environmental transmission, the final outcome is a strain that predominantly transmits directly from one host to another. In other situations in which dimorphic singularities do not exist, branching may lead to evolution of a parasite that excels in transmission via the environment.



(a) (b) (c)

Figure 3: (a) Pairwise invasibility plot for $u = 2.7, v = 0.025$ and $\theta = \frac{0.2\alpha}{0.3\alpha+1}$. The remaining parameters and trade-offs are as in Figure 1. Branching point depicted with a green, repeller with a red and a CSS with a blue dot. (b) Regions of coexistence (in white) along with isoclines and arrows showing the direction of dimorphic evolution. (c) Simulation of evolutionary dynamics showing convergence to the branching point, subsequent diversification, extiction of one of the strains and final convergence to the CSS.

Suppose now that a dimorphic evolutionary singularity does exist. Since neither of the traits that form a dimorphic singularity can be found in parameter regions where both D and E are increasing (or decreasing; see (17)), dimorphic singularities remain inbetween the maxima of D and E. Hence, when an initially monomorphic pathogen population branches, one of the strains will begin to specialize on direct transmission and the other strain will excel in environmental transmission. However, both of the strains will remain suboptimal when compared to the pure-direct or pure-environmental transmission model. Since our model includes at most two environmental feedback variables we know that, if a dimorphic singularity exists, it is uninvadable whenever it is convergence stable. In other words, no further diversification is possible.

How does a dimorphic singularity change when we vary the strength of direct or environmental transmission? To obtain some information, we return to the examples of the previous section and choose three values of u that according to Figure 1 yield branching: $u = 5, u = 6.1$ and $u = 7$. Thus, we keep the trade-offs pertaining to direct transmission fixed, while the strength of environmental transmission is changed by varying u in (14). In Figure 4 we present mutual invadability plots corresponding to PIPs in Figures 1 (c)-(e), along with the isoclines and the arrows delineating the direction of dimorphic evolution. In addition, we present in Figures 4 (d)-(f) the corresponding graphs of $D(\alpha)$ and $E(\alpha)$. We observe that, when longevity is reached faster (u is high), the peak of environmental transmission is reached sooner and is also higher. The upper of the two values in a dimorphic singularity (which is better at environmental transmisson) decreases, while the virulence of the strain that specializes on direct transmission increases slightly. In other words, the more severe strain becomes less virulent, while the virulence

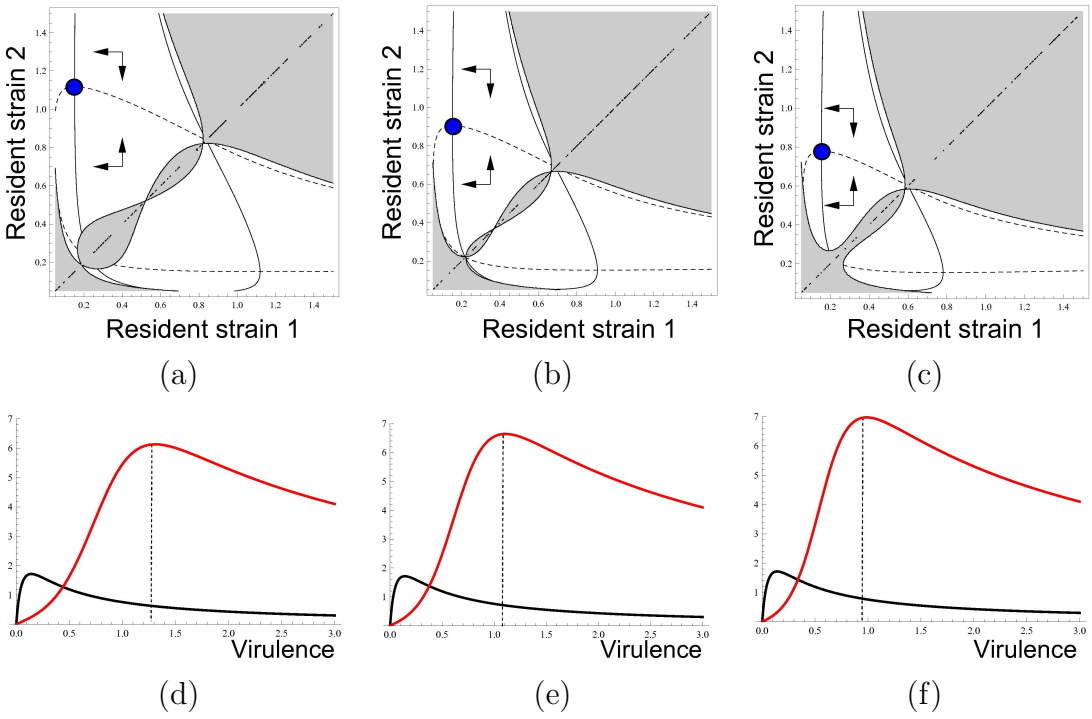


Figure 4: Figures (a), (b) and (c) show regions of coexistence (in white) and isoclines along with arrows that depict the direction of dimorphic evolution. These trait evolution plots correspond to pairwise invasibility plots in Figure 1, with (a) $u = 5$, (b) $u = 6.1$ and (c) $u = 7$. The dimorphic singularity, depicted by a blue dot, is the intersection of the two isoclines: for $u = 5$ the dimorphic singularity is at $(0.151, 1.12)$, at $(0.153, 0.91)$ for $u = 6.1$ and $(0.154, 0.78)$ for $u = 7$. Figures (d), (e) and (f) show the graphs of $D(\alpha)$ (in black) and $E(\alpha)$ (in red) for, respectively, $u = 5$, $u = 6.1$ and $u = 7$.

of the mild strain increases slightly as the strains move closer to each other.

Discussion

Pathogens that spread via different transmission routes frequently face conflicting selection pressures that arise due to contrasting adaptations required for enhancing the different modes of infection spread. We have shown that multiple transmission modes, in particular direct and environmental transmission, can induce the evolution of strain diversity. If the two transmission modes require contrasting adaptations of the pathogen, then a single ancestral strain may split into two lineages via evolutionary branching, and the emerging two strains may subsequently specialise on separate transmission routes.

The essential feature of all models exhibiting coexistence or evolutionary branching is the presence of at least two environmental feedback variables, i.e., of at least two variables of population dynamics through which the coexisting strains affect each other (Tilman (1982); Dieckmann and Metz (2006); Meszéna et al. (2006)). In our model, the two feedback variables are the density of susceptibles (S) and the density of free pathogens (P). The density of susceptibles affects reproduction via both transmission modes, whereas the density of free pathogens acts through the incidence function $g(P)$ of the environmental transmission mode. It is essential that $g(P)$ is a non-linear function (cf. section Evolutionary invasion analysis and Day (2002)) such that the density of free pathogens influences the probability that any given free pathogen successfully infects a susceptible host. Contrary to the simplest assumption of mass action incidence, non-linear incidence functions g have the capacity to reflect the saturation of the rate at which susceptibles encounter free pathogens at high environmental loads and can capture the fact that, at low prevalence, free parasites may present a negligible risk of indirect infection.

To explain how a non-linear incidence leads to coexistence we note that the fitness function in equation (5) gives variable weights to the two transmission modes: the environmental transmission term E is weighted by the factor $G(P) = g(P)/P$, relative to the direct transmission term D. When $g(P)$ is concave, then $G(P)$ is decreasing in P. A resident strain more specialised to environmental transmission produces a high equilibrium density of free pathogens (P) and therefore a low weight $G(P)$ to the environmental transmission term, which favours an alternative strain that specialises more on direct transmission. Conversely, a resident strain adapted to direct transmission equilibrates the density of free pathogens at a lower value, whereby the environmental transmission term gets a higher weight and a strain more adapted to environmental transmission gains an advantage. The variable weight of the two terms thus leads to coexistence by mutual invasibility.

Our model exhibits a remarkable degree of flexibility. In our general analysis, we allowed for an arbitrary number and shape of trade-off functions connecting the evolving pathogen trait to the pathogen's demographic parameters $(\alpha, \beta, \rho, \theta, \gamma, \sigma)$ as well as an arbitrary incidence function $g(P)$. Under such flexibility, the traditional methods of analysis are less straightforward to apply. Instead, we relied on a simple observation (Bowers et al. (2005); Kisdi (2006)) that evolutionary branching happens for a range of trade-off functions provided that coexistence by mutual invasibility is possible near the

singular trait value. We found that the latter condition holds for all concave incidence functions $g(P)$, provided that the infectivity of free pathogens does not vary too steeply with the evolving trait of the pathogen (i.e., $|\gamma'|$ is not too large). We thus conclude that evolutionary branching is possible under very mild restrictions on a rather flexible model. Within these restrictions, there is always a range of trade-off convexities where evolutionary branching occurs.

Concrete examples for evolutionary branching are shown in Figure 1. In this example, we considered an important special case where the evolving trait is virulence, traded-off against three other traits: infectivity via direct host-to-host transmission (β), the rate of shedding of free pathogens (θ), and the decay rate of free pathogens (σ). The model exhibits a rich pattern of bifurcations with evolutionary branching in a substantial part of the parameter region (see Figure 2). By way of examples we have shown that evolutionary branching may lead to evolutionary coexistence of two strains with markedly different virulence levels. Our findings may thus explain the coexistence of high and low virulence strains that is observed in several infectious diseases utilising multiple transmission modes, such as avian influenza (see Olsen et al. (2006) and Chen et al. (2005)) or *Vibrio cholerae* (Pascual et al. (2002)).

In addition to the evolution of pathogen populations in ecological communities (such as influenza in human or avian populations), our framework can be applied to the within-host setting to study, for example, the evolution of HIV within one infected host. Indeed, recent results show that viruses can be transmitted directly from one cell to another as well as via free viruses, which is likely to affect treatment (see Deeks (2011); Sigal et al. (2011)). Alizon and Boldin (2010) have recently shown that branching within one HIV infected host can be interpreted as the co-receptor switch (Regoes and Bonhoeffer (2005)).

We use Adaptive dynamics to explore not only whether evolutionary branching is possible but also the coevolution of two coexisting strains after evolutionary branching (Geritz et al. (1998)). Since there are only two environmental feedback variables, no more than two strains can coexist (Tilman (1982)); and if there is a dimorphic singularity, one can find it with a simple graphical method (see also Svennungsen and Kisdi (2009)). Note, however, that a dimorphic ESS need not exist. In the example of Figure 3, evolutionary branching is followed by extinction such that eventually the evolving pathogen arrives at a single-strain ESS, even though its evolution had an "excursion" through dimorphisms. Evolutionary branching is not sufficient for coexistence to persist on evolutionary time scales (see also Geritz et al. (1998) and Geritz et al. (1999) for examples in the context of competition models).

For virulence management, it is an important question whether some of the coexisting strains in a diverse pathogen population evolve higher virulence than a single strain would evolve in isolation, i.e., whether diversity promotes the existence of highly virulent strains (Roche et al. (2011)). Suppose that the fitness via direct transmission only (D) and the fitness via environmental transmission only (E) are unimodal functions of virulence, and let α_d^* and α_e^* be the strains that are optimal in direct and environmental transmission, respectively. Outside the interval spanned by these two optima both direct and environmental transmission select in the same direction and hence no trait value can be singular;

any dimorphic singularity must thus be such that both strains are inbetween α_d^* and α_e^*. Whether α_d^* is smaller or greater than α_e^* depends on the trade-off functions and cannot be established *a priori*. Day (2002) however argues that environmental transmission is likely to select for higher virulence than direct transmission ($\alpha_e^* > \alpha_d^*$). It follows then that the highest virulence (α_e^*) evolves when transmission is solely environmental and the pathogen thus remains monomorphic. In dimorphic pathogen populations, the more virulent strain evolves near α_e^* (but remains at least somewhat below) if the two optima are strongly separated such that the two strains are forced to adapt to alternative transmission modes. If the optima α_d^* and α_e^* are less separated, then each strain benefits from retaining some capacity to reproduce also via the transmission mode it is less adapted to, and therefore evolution comes to a halt before the strains get near to their respective optima (this is shown in Figure 4). Direct transmission therefore decreases the evolved virulence of the more virulent strain of a dimorphism, and this effect is stronger if the two optima are less separated. This pattern of dimorphic evolution is similar to the evolution of specialists adapting to alternative habitats in spatially heterogeneous environments (e.g. Meszéna et al. (1997); Kisdi and Geritz (1999)).

Evolutionary bi-stabilities leading to alternative ESSs represent a distinctly different mechanism for the evolution of a virulent strain (cf. Figure 1b). In this case, the pathogen population remains monomorphic. With a deep fitness valley between α_d^* and α_e^*, there is no "compromise" generalist strategy that would be able to utilise both transmission modes sufficiently well to act as an initial point of diversification. Instead, the initial strain evolves towards one of the two transmission peaks. With $\alpha_e^* > \alpha_d^*$, high virulence evolves if the initial strain is virulent enough to be attracted to the singularity near the peak of environmental transmission. Since the singularity is always inbetween α_d^* and α_e^*, direct transmission always decreases the evolved virulence of a strain that is adapted mostly to environmental transmission; this effect is however weak because of the strong separation of the fitness peaks. An evolutionary bi-stability is therefore likely to lead to the evolution of a pathogen adapted to one transmission mode and performing weakly in the other. Further adaptations in other pathogen traits can reinforce this pattern until one transmission mode is lost for the pathogen.

Comparison to previous models

Maintenance of strain diversity has been well studied for strictly directly transmitted infectious diseases, where diversity has often been attributed to multiple infections of the host or to various kinds of host heterogeneity. Intrinsic variation in host properties can induce evolutionary branching akin to the evolution of diversity in multiple habitats (Gudelj et al. (2004); Gandon (2004); Osnas and Dobson (2012)). Similarly, hosts with different vaccination statuses (André and Gandon (2006)) or with different levels of evolved resistance (Best et al. (2010)) can promote the evolution of multiple pathogen strains. Multiple infections of individual hosts sustain strain variety (Nowak and May (1994); Mosquera and Adler (1998)) and promote the evolution of strain diversity (Alizon (2008); Mosquera and Adler (1998); Boldin and Diekmann (2008); Boldin et al. (2009)),

essentially by creating a number of host classes that differ in their infection status. To exclude these known mechanisms promoting diversity, our model assumed a homogeneous population of hosts with perfect cross-immunity between pathogen strains.

A different mechanism underlying strain diversity in single-infection models involves the transmission-virulence trade-off and density dependence in the host's natural death rate (Andreasen and Pugliese (1995); Pugliese (2002); Svennungsen and Kisdi (2009)). We excluded this mechanism of coexistence by assuming that the host population is regulated via its birth rate. For simplicity, we assumed a constant population birth rate (b), which corresponds to the *per capita* birth rate being inversely proportional to population size.

The role of alternative transmission modes has been studied in the case of vertically versus horizontally transmitted pathogens. Lipsitch et al. (1996) pointed out that these two transmission modes allow for the coexistence of strains, whereas Dhirasakdanon and Thieme (2009) analysed the conditions for coexistence and found that it is possible even if the vertically transmitted strain is not viable by itself. Ferdy and Godelle (2005) showed that evolutionary branching can produce an avirulent, vertically transmitted strain that coexists with a virulent, horizontally transmitted strain. This result is broadly similar to our finding that contrasting selective forces acting in two different transmission modes can lead to evolutionary branching of pathogens.

Two previous studies investigated the evolution of pathogens with direct and environmental transmission (Day (2002); Roche et al. (2011)). Day (2002) assumed mass action for both transmission modes, which implies a single environmental feedback variable and therefore an optimisation model where coexistence and evolutionary branching are not possible (cf. section Evolutionary invasion analysis; Metz et al. (2008)). Assuming $g(P) = P$ implies $G(P) = g(P)/P = 1$ in equation (5), which leads to fixed weights of the two transmission terms. Coexistence, however, relies on variable weights the two transmission modes get via $G(P)$ (see above). We note that also with other mechanisms maintaining diversity, certain specific choices simplify the models such that they no longer support coexistence. For example, the model of Regoes et al. (2000) includes multiple host types but, contrary to the multi-host models cited above, it does not permit coexistence of pathogen strains due to a constant ratio of hosts types. Similarly, partial vaccination leads to pathogen diversity in the study of André and Gandon (2006) but not in the simpler model of Gandon et al. (2003) (see Svennungsen and Kisdi (2009) for further discussion). In our model, the choice of mass action is a simplification that fundamentally alters the properties of the model.

More recently, Roche et al. (2011) studied the evolution of virulence for pathogens utilising direct and environmental transmission. However, their study contains several flaws, which we wish to discuss here. Roche et al. (2011) investigate a special case of our model in (2) with the incidence function $g(P) = P/(P+\kappa)$ and with very specific choices of trade-offs. Their simulations demonstrate coexistence, but they do not find evolutionary branching points. They conclude that their model "exhibits an evolutionary bi-stability yielding a coexistence of two strains". This conclusion is incorrect; bi-stability does not lead to coexistence. The simulation in Figure 4b of Roche et al. (2011) is especially misleading as the splitting evolutionary tree suggests branching at a singularity they

identify as a repeller. In this simulation, the initial pathogen population was perched atop the repeller. There is no biological reason the initial virulence of a pathogen would equal the singular virulence; and should the simulation start at a different virulence, the population would not branch but would evolve away from the repeller. In contrast, the evolutionary branching points we find in the model are attractors of single-strain evolution. For diversity to evolve from a single ancestral strain, the pathogen first has to evolve to the singularity where splitting will occur, and this happens only if the singularity is an evolutionary branching point (Geritz et al. (1998)).

Further, Roche et al. (2011) claim that coexistence is possible only if virulence is an evolving trait. In Figure B1 in Supplementary material B, we show an example of evolutionary branching leading to coexistence with fixed virulence ($\alpha = 0$), where β and θ are traded off against σ according to the trade-offs assumed by Roche et al. (2011). Fixing virulence and introducing trade-offs between direct and environmental transmission via another evolving trait does not change the feedback structure and therefore does not exclude coexistence and evolutionary branching.

To reconcile coexistence with the opposing result of Day (2002), Roche et al. (2011) highlight Day's assumption of a fixed decay rate σ and attribute coexistence to relaxing this assumption. In Figure B2 of Supplementary material B, we show a counterexample, where evolutionary branching occurs with a fixed σ. As we argued above, the true difference is in the feedback structure of the models and Roche et al. (2011) have seriously misapprehended the conditions necessary for the evolution and maintenance of pathogen diversity. In Supplementary material B, we point out some further modeling mistakes made by Roche et al. (2011).

Conclusion and outlook

Our study highlights the role of incidence in the evolution of pathogen diversity. Pathogen populations that are transmitted in host populations in which contact rates are not simply proportional to population densities tend to exhibit richer evolutionary dynamics. In this study, we considered host-pathogen systems in which the incidence for direct transmission is proportional to the host density while assuming a concave incidence function for environmental transmission. These simplifications do not to restrict the possible evolutionary scenarios and all monomorphic evolutionary singularities (CSSs, branching points and repellers) appear in the model (cf. Figure 2), which is in stark contrast with optimisation under mass action law (Day (2002)). Allowing for arbitrary incidence functions in both transmission modes would make the model difficult to analyse with current methods. In a future paper (Kisdi and Boldin (in preparation)), we present new techniques to investigate pathogen evolution in the context of the more general model summarized in eq. (1). These new techniques allow us to study the evolutionary dynamics of pathogens in host populations where incidence functions for direct and environmental transmission depend arbitrarily on host population and pathogen densities.

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