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REVIEW

Evolution of spatially structured host–parasite interactions

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Abstract

Spatial structure has dramatic effects on the demography and the evolution of species. A large variety of theoretical models have attempted to understand how local dispersal may shape the coevolution of interacting species such as host–parasite interactions. The lack of a unifying framework is a serious impediment for anyone willing to understand current theory. Here, we review previous theoretical studies in the light of a single epidemiological model that allows us to explore the effects of both host and parasite migration rates on the evolution and coevolution of various life-history traits. We discuss the impact of local dispersal on parasite virulence, various host defence strategies and local adaptation. Our analysis shows that evolutionary and coevolutionary outcomes crucially depend on the details of the host–parasite life cycle and on which life-history trait is involved in the interaction. We also discuss experimental studies that support the effects of spatial structure on the evolution of host–parasite interactions. This review highlights major similarities between some theoretical results, but it also reveals an important gap between evolutionary and coevolutionary models. We discuss possible ways to bridge this gap within a more unified framework that would reconcile spatial epidemiology, evolution and coevolution.

Introduction

Biotic interactions affect the ecology and the demography of species. Infectious diseases, in particular, can have dramatic consequences on the dynamics of their host populations (Anderson & May, 1991; Schmid-Hempel, 2011). Such antagonistic interactions have led to the evolution of a very diverse range of defence strategies in host populations (Agnew *et al.*, 2000; Labrie *et al.*, 2010; Schmid-Hempel, 2011), as well as complex counter-defence strategies in parasite populations (Thompson, 2005; Samson *et al.*, 2013). A large theoretical literature has developed in an attempt to formalize these complex coevolutionary dynamics. It may be difficult to unearth the links among the sheer variety of models and theoretical approaches that have been proposed. In particular, a major difference between models is whether or not they allow for feedbacks between evolution and demography. The absence of feedback has its virtues: removing the complexity induced by demography highlights evolutionary dynamics occurring through genotype frequency changes. This approach, however, is disconnected from mathematical epidemiology and overlooks major selective forces acting on the host or on the pathogens (Day & Gandon, 2007; Boots *et al.*, 2009).

Another factor affecting the evolution of species is the influence of spatial structure. In a spatially structured environment, individuals are interacting and are competing mostly with related individuals. Inclusive fitness theory (Hamilton, 1964; Frank, 1998a; Rousset, 2004) formalizes how these interactions can affect the evolutionary dynamics of many social traits like altruism (Lehmann & Rousset, 2010), sex allocation (West, 2009) or dispersal (Hamilton & May, 1977). Many different models have been developed but, again, a major distinction appears between those allowing demography to feedback on evolution or not (Rousset & Ronce, 2004; Lion & van Baalen, 2008; Lion *et al.*, 2011).

Our aim is to review and discuss different attempts at modelling the evolution of host–parasite interactions in spatially structured environments. Indeed, both biotic interactions and spatial structure are major factors in

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the environment of any species. Many studies have focused on the demographic consequences of combining these two factors. In particular, migration among multiple populations is generally viewed as a way to maintain the coexistence of both the host and the parasite at a larger spatial scale (Nicholson, 1933; Tilman & Kareiva, 1997; Hassell, 2000; Jansen & de Roos, 2000; Hagenaars *et al.*, 2004). Metapopulation dynamics may thus be a way to understand the maintenance of host populations that would be driven to extinction by their pathogens in a well-mixed environment (but see Wodarz *et al*. (2013) showing that nearest neighbour interactions may also have the opposite effect). Here, however, we will concentrate on the evolutionary and coevolutionary dynamics of interacting species in space. We will review attempts to model (1) the evolution of parasite life-history traits, (2) the evolution of various host defence strategies against parasites and (3) host–parasite coevolution in space. At the end of each section, we also present some experimental and empirical evidence supporting the influence of spatial structure on the interactions between parasites and their hosts. Throughout the study, we restrict our attention to spatial structure resulting from localized host or parasite dispersal. It is often difficult to compare previous theoretical studies when they are derived under very different sets of assumptions. Here, we discuss these studies in the light of a simple epidemiological model that has been widely used in theoretical studies (Fig. 1). We use this reference model to explore the relative influence of host and parasite dispersal rates on the evolutionary and coevolutionary outcomes of the interaction. Hence, a common thread to the various sections of the article will be to analyse the potentially different impacts of host versus parasite dispersal rates on (i) the demography of the population, (ii) the prevalence of infection and (ii) the evolution of host and parasite traits. This reveals major similarities between the effects of spatial structure on parasite and host evolution, but we also point out important gaps between evolutionary and coevolutionary models. We discuss the possible ways to bridge these gaps within a more unified framework that reconciles spatial epidemiology and evolution.

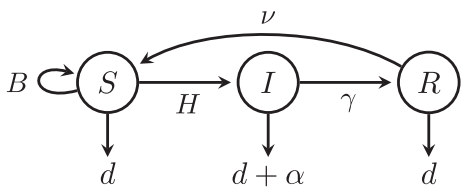


Fig. 1. General life cycle used throughout the study. $H = \sigma\beta[I|S]$ denotes the force of infection, where σ is the susceptibility to the disease, β is disease transmissibility, and $[I|S]$ is the overall density of infected hosts experienced by a susceptible host. Note that infected hosts do not reproduce.

Parasite evolution

Spatial selection gradient

A large body of theory has investigated the evolution of parasite life-history traits such as transmission or virulence (defined as disease-induced mortality). In a spatially or socially structured host population, different parasite genotypes may experience different local environments. For instance, two parasite strains may have access to different levels of resource if they experience different local densities of susceptible hosts. To understand how this may affect the selective pressures on the parasite's life-history traits, let us consider a spatial version of the classical susceptible–infected–recovered (SIR) model that we use as a common thread throughout the article (Fig. 1).

We consider a network of sites, where each site can be either empty or occupied by a susceptible (S), an infected or a recovered (R) host. Infected hosts can either harbour a wild-type strain of the parasite (I) or a mutant strain (I^*). Parasite transmission occurs at rate β for the wild-type strain and β^* for the mutant strain (the '*' notation will be used throughout the study to refer to the mutant strain). Hosts infected by the wild-type (resp. mutant) parasite leave the infected class at rate $\delta = d+\alpha+\gamma$ (resp. δ^*), through either death or recovery (Anderson & May, 1982). Parasite transmission can be either local (to a susceptible neighbour) or global (to a random susceptible host in the population) with probability g_P. Finally, susceptible hosts can reproduce either locally (to a neighbouring empty site) or globally (to a random empty site) with probability g_H. Hence, host reproduction is density-dependent. With these assumptions, the change in the frequency f_P of the mutant type is (see Box 1)

$$\frac{df_P}{dt} = f_P(1 - f_P)(\Delta[\beta S] - \Delta\delta) \qquad (1)$$

The quantity $\Delta[\beta S]$ is the difference between the rates of new infections by the mutant and wild-type parasites. Similarly, $\Delta\delta$ is the difference between the death rates of the hosts infected by the mutant versus wild-type parasites. Note that equation (1) is exact as long as the only three processes affecting the density of infected hosts are death, recovery and horizontal transmission from a pool of susceptible hosts. With other sources of newly infected hosts (e.g. vertical transmission), additional terms would need to be taken into account. However, these biological complications are nearly always ignored in the literature we review.

Under the assumption that the mutant is initially rare the host population infected by the wild-type parasite can be assumed to be at equilibrium, and we have $(1 - g_P)q_{S/I} + g_P p_S = \delta/\beta$, where p_S is the global density of susceptible hosts, and $q_{S/I}$ is the local density of susceptible hosts around a host infected by the wild-type

Box 1: Definitions of variables

General variables	
p_x	global density of sites in state x: empty (p_o), filled with a susceptible host (p_S) or an infected host (p_I)
$q_{x/y}$	local density of sites in state x in the neighbourhood of an average site in state y ex: $q_{S/I}$ is the average local density of uninfected hosts in the neighbourhood of an infected host
g_P, g_H	proportion of global migration among newly produced parasites or hosts, respectively
Parasite evolution	
f_P	frequency of parasite mutant strategy
I, I^*	hosts infected by a wild-type or mutant parasite, respectively.
$[\beta S]^* = \beta^*[(1-g_P)q_{S/I^*} + g_P p_S]$	rate of new infections by the mutant parasite. Similar expression for $[\beta S]$.
$\Delta[\beta S] = [\beta S]^* - [\beta S]$	difference between the rates of infection of the mutant and the wild type
$\Delta\delta = \delta^* - \delta$	difference between the death rates of the mutant and the wild-type parasite.
Host evolution	
f_H	frequency of host mutant strategy.
S, S^*	wild-type or mutant uninfected hosts, respectively.
I, I^*	wild-type or mutant infected hosts, respectively.
$[o\|S] = (1\text{-}g_H)\, q_{o/S} + g_H p_o$	overall density of empty sites as experienced by a susceptible host.
$B^* = b^*[o\|S]$	rate of reproduction of the mutant host. Simlilar expression for B.
$\Delta B = B^* - B$	difference between the reproduction rates of the mutant and the wild-type hosts.
$\Delta D = d^* - d$	difference between the death rates of the mutant and the wild-type hosts.
$[I\|S^*] = (1-g_P)q_{I/S^*} + g_P p_I$	overall density of wild-type infected hosts, as experienced by mutant susceptible hosts. Similar expression for $[I^*\|S^*]$ and $[I\|S]$.
$H^* = \sigma^*(\beta[I\|S^*] + \beta^*[I^*\|S^*])$	rate of infection experienced by a mutant susceptible host. Similar expression for H.
$\Delta H = H^* - H$	difference between the rates of infection experienced by the mutant and the wild-type hosts.

parasite. Then, some algebra shows that the mutant parasite will be favoured by selection if:

$$\left(\frac{1}{R_P} - \frac{1}{R_P^*}\right) + (1-g_P)(q_{S/I^*} - q_{S/I}) > 0 \qquad (2)$$

where q_{S/I^*} is the local density of susceptible hosts around a host infected by a mutant parasite. When infections are global ($g_P = 1$), only the first term remains, and we recover the classical prediction that, in the absence of spatial structure, parasites should evolve to maximize their expected life-time production of infectious particles $R_P = \beta/\delta$. This is a version of the marginal value theorem (Charnov, 1976) where the evolutionarily stable strategy of host exploitation is the one that minimizes the equilibrium density of susceptible hosts (the resource, $\hat{p}_S = \delta/\beta$). In other words, the parasite that creates the worst possible world is selected for (pessimization principle, Mylius & Diekmann (1995), Metz *et al.* (2008)).

When infections can occur locally, the second term is nonzero and represents an additional selective pressure on the mutant, which is positive (resp. negative) if the local density of susceptible hosts experienced by the mutant parasite (q_{S/I^*}) is higher (resp. lower) than that experienced by the resident parasite ($q_{S/I}$). This term measures the intensity of local competition between parasites for susceptible hosts. One may expect that a mutant parasite with a higher reproductive output ($R_P^* > R_P$) would experience a lower local density of susceptible hosts than the resident parasite ($q_{S/I^*} < q_{S/I}$). Hence, an increase in individual reproduction has an opposite effect on the spatial and nonspatial selective pressures on parasites. Based on this reasoning, one expects spatial structure to favour more prudent strategies of host exploitation, leading to reduced transmission or virulence compared to the well-mixed populations. However, as we shall see, this semi-verbal argument can sometime be misleading.

Genetic and epidemiological structuring

Two seemingly different explanations have been proposed in the literature to explain the evolution of parasite prudence in space. First, because spatial structuring leads to the local build-up of relatedness among parasites infecting neighbouring hosts, kin selection has been argued to select for more prudent exploitation of the local host supply. In other words, parasite prudence can be interpreted as an altruistic trait (Frank, 1996; van Baalen, 2002; Lion & van Baalen, 2008). This argument is a direct extension of classical kin selection models of multiple infections (Frank, 1992, 1996; van Baalen, 2002): higher relatedness among parasites can be expected to select for reduced virulence.

Second, early epidemiological models (Boots & Sasaki, 1999, 2000; Haraguchi & Sasaki, 2000) have found the same general pattern, but emphasized another mechanism, termed 'self-shading', by which the clustering of infected individuals reduce their effective transmission to susceptible hosts (Messinger & Ostling, 2013).

Importantly, both explanations revolve around the $q_{S/I^*} - q_{S/I}$ term in the selection gradient (2), and merely emphasize different aspects of the same process. The kin selection argument puts forward the genetic structuring of the parasite population (the relatedness between parasites infecting neighbouring hosts, see Box 2), while the self-shading argument highlights the role of epidemiological structuring (the spatial distribution of susceptible and infected hosts). However, local parasite dispersal will affect both genetic and demographic structuring. Because of local infections, in a spatially structured environment, parasites infecting a cluster of hosts tend to be related (genetic structuring). At the same time, infected hosts will tend to have access to less susceptible hosts (epidemiological structuring). In the end, both components will affect the (inclusive) fitness of the parasite. This has been clarified either through a more traditional inclusive fitness analysis (Wild *et al.*, 2009) or through an invasion analysis based on spatial moment equations (Lion & Boots, 2010).

In Box 2, we show how these two views on pathogen evolution can be reconciled. In general, the competition term $q_{S/I^*} - q_{S/I}$ will be affected by the coupled dynamics of genetic and epidemiological structuring. However, if epidemiological dynamics are fast enough (separation of time scales) and mutations have small phenotypic effects (weak selection), quasi-equilibrium approximations can be used to decouple the two and express local competition for susceptible hosts in terms of measures of genetic structuring and of measures of epidemiological structure at equilibrium (Lion & Boots, 2010). When selection is weak, the relevant genetic structure of the parasite population can be captured using r, the relatedness between parasites infecting neighbouring hosts (see Box 2). In general, relatedness will depend on parasite and host dispersal rates, life-history traits and the structure of the contact network, because these processes all affect the probability that two parasites share the genes of a common ancestor (Rousset, 2004). But the epidemiological structure, e, also affects selection on the parasite. The direction of evolution is determined by the balance between these two factors (see Box 2).

It is important to note that different parasite life cycles have contrasting effects on genetic and epidemiological structure. This explains the strikingly different evolutionary outcomes that are observed in even the simplest epidemiological models, under the assumption

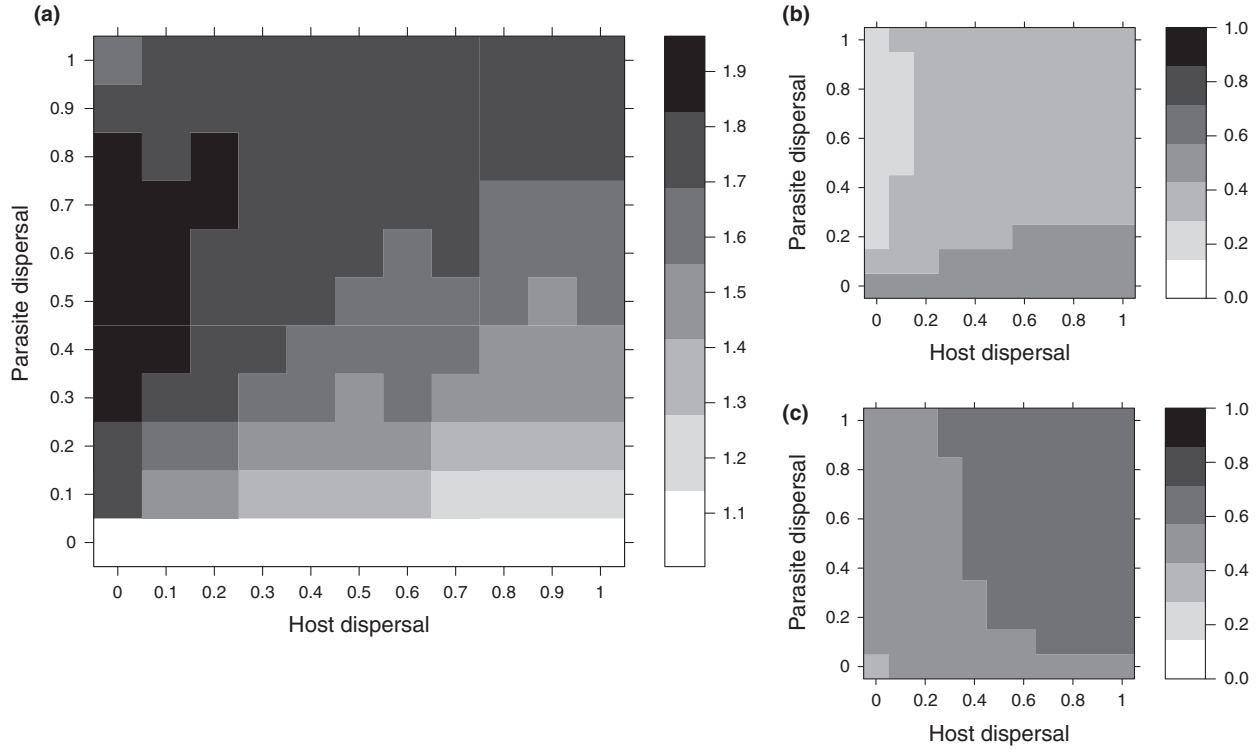


Fig. 2. Evolution of parasite traits. (a) Mean virulence. (b) Total host density, p_S+p_I. (c) Disease prevalence $p_I/(p_S+p_I)$. Stochastic simulations were run on a square lattice with the same parameters as in fig. 1b of Lion & Boots (2010): $b = 8$, $d = 1$, $\beta(\alpha) = 20 \log(1+\alpha)$, $\gamma = 0$. The simulations were initialized with 11 strains with virulence between 0 and 4. Mutations between strains with adjacent values occurred at rate $\mu = 0.001$. For each combination of host and parasite dispersal rates, the mean value between $t = 750$ and $t = 1000$ was computed and averaged across 6 runs.

of a concave-down trade-off between transmission and virulence (Lion & Boots, 2010).

In our baseline model (Fig. 1), parasites are predicted to be more prudent when infections are fully local, but virulence can be maximal at intermediate parasite dispersal when host dispersal is sufficiently local (Fig. 2; see also Kamo *et al*. (2007), Webb *et al*. (2013)). Lion & Boots (2010) give an analytical underpinning for this result and show that whether or not prudence evolves in space in this model depends on whether parasite relatedness is greater than a threshold determined by the epidemiological structure (Box 2). However, the balance between genetic and epidemiological structure may be affected by other life-history traits such as host dispersal (Fig. 2a) or host fecundity. In contrast with nonspatial SI (S) or SIR(S) host–parasite interactions, where the evolutionarily stable level of virulence is predicted to depend only on host mortality, recovery and the shape of the trade-off between transmission and virulence (Frank, 1992), host fecundity has been shown to affect the evolution of parasite life-history traits in space (Messinger & Ostling, 2013). Indeed, the strength of the spatial selective effect decreases when the local density of empty sites experienced by an infected individual ($q_{o/I}$) decreases (Lion & Boots (2010); Box 2). Any process that reduces this density (such as high host fecundity) should therefore select for levels of host exploitation that are closer to the corresponding nonspatial prediction (Box 2).

Examples of this process can be found in the theoretical literature. When host fecundity is large ($B \to \infty$) and there is no recovery ($\gamma = 0$), we recover the simple susceptible–infected–susceptible (SIS) model with constant host population (Claessen & de Roos, 1995). In this case, parasite dispersal is found to have no effect on the evolutionarily stable level of host exploitation (Lion & Boots, 2010). Spatial structure merely slows down the speed at which the ESS is reached. Note that, although Lion & Boots (2010) have focused on a trade-off between transmission and recovery, similar results hold for a transmission–virulence trade-off.

When host fecundity is large and recovery is nonzero, however, the dynamics converge towards the susceptible–infected–recovered model with constant host population size (SIRS). In this case, the situation is different, because the strength of the spatial effect is now inversely proportional to the rate of immunity loss, ν. Under a transmission-recovery trade-off (van Baalen, 2002; Lion & Boots, 2010), parasite exploitation of the host is shown to decrease monotonically as infections become more local.

Other studies have investigated the joint role of recovery and host demography and showed that increased recovery rates tend to weaken the spatial effect of demographic turnover (Webb *et al*., 2013). It would be interesting to examine these results using the same formalism as Box 2. Finally, we note that, although most studies have considered a trade-off between transmission and the duration of infection, spatial structure may also affect the evolution of parasite traits under other constraints, leading to potentially complex evolutionary dynamics. For instance, evolutionary bistability has been demonstrated in a model combining host demography and immunity under a virulence-recovery trade-off (Boots *et al*., 2004; Webb *et al*., 2013).

Emergent trade-offs

Many studies assume the classical concave-down trade-off between transmission and virulence, which implies that an increase in parasite transmission can only be bought at the expense of reduced host survival. In contrast with nonspatial theory, which predicts evolution for maximal virulence with linear or concave-up trade-offs, the additional selective pressure due to local competition for susceptible hosts allows intermediate levels of host exploitation to evolve in spatially structured populations (Boots & Sasaki, 1999, 2000; Haraguchi & Sasaki, 2000; Kamo *et al*., 2007; Messinger & Ostling, 2013). Furthermore, in the absence of a trade-off between transmission and virulence, spatial structure has been found to select for intermediate transmission rates (Rand *et al*., 1995; Haraguchi & Sasaki, 2000; Messinger & Ostling, 2013). Interestingly, spatial structure can also lead to emerging relationships between parasite life-history traits in the absence of physiological trade-offs (Read & Keeling, 2003; van Ballegooijen & Boerlijst, 2006) or put constraints on the evolution of parasite manipulation of host dispersal in the absence of cost (Lion *et al*., 2006). What is often overlooked, however, is that these emerging constraints on life-history traits depend on the type of spatial structure. For instance, transmission evolves to intermediate levels on a square lattice, but not on a random network, where maximal transmission is selected for (Lion & Boots, 2010). This indicates that large-scale spatial correlations play a key role in these evolutionary outcomes. This is further confirmed by the fact that the first-order spatial approximation used in Lion & Boots (2010) fails to predict these intriguing patterns. The link between lattice and metapopulation models also deserves further study. For instance, Wild *et al*. (2009)'s island model does not predict that virulence peaks at intermediate parasite dispersal, as Kamo *et al*. (2007), Lion & Boots (2010), despite a similar life cycle. A possible explanation is that host migration rate in Wild *et al*. (2009)' study is too high, as Fig. 2 shows that virulence only peaks at intermediate parasite dispersal when host dispersal is low.

Multiple infections

Nonspatial models of multiple infections have shown that within-host competition between parasite strains often selects for higher levels of host exploitation

Box 2: Graphical interpretation

For models following the life cycle in Fig. 1, the selection gradient is proportional, to a first-order approximation, to

$$\mathcal{S} = [1 - (1 - g_P)u(r - e)]\frac{\partial\beta}{\beta} - \frac{\partial\delta}{\delta},$$

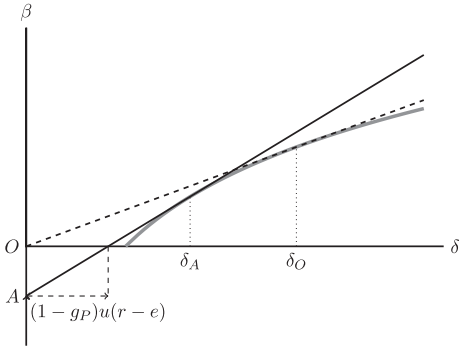
where $\partial\beta$ and $\partial\delta$ are short-hand notations for the partial derivatives of the traits with respect to the mutant's trait, evaluated at neutrality. In this form, it is clear that a unit marginal increase in transmission is not as valuable as a unit marginal decrease in host mortality. Compared to survival, the investment into transmission must be discounted by a quantity $(1-g_P)u(r-e)$, where $r = q_{I^*/I^*} - q_{I^*/I}$ represents between-host relatedness among parasites (Lion & Gandon, 2009; Lion & Boots, 2010), e is a measure of epidemiological structure, and u measures the strength of the spatial selective pressure. Both e and u depend on the specificities of the pathogen life cycle (see table below).

Graphically, this means that the tangent at the ESS intersects the x-axis at $(1-g_P)u(r-e)$. If this quantity is zero, the marginal value theorem is recovered. If it is positive, it is clear from the figure that, at the ESS, host exploitation is more prudent than predicted by nonspatial theory. Hence, a simple criterion for the evolution of parasite prudence is whether

$$r > e$$

that is whether genetic structuring is above a threshold determined by the epidemiological structure of the population. For a rare mutant parasite, relatedness is simply given by q_{I^*/I^*}, the local density of hosts infected by the mutant parasite experienced by a focal host infected by the mutant parasite.

It is worth pointing out that the strength of this effect is proportional to the scaling factor u. When u is vanishingly small, the model predicts that parasites should exploit their host as predicted by nonspatial theory, even if $r>e$. In particular, high rates of immunity loss in a SIRS model or high host fecundity in a SI model tend to decrease the strength of the spatial selective effect, measured by u (Lion & Boots, 2010). The expressions of u and e when $g_H = g_P = 1$ for various limits of the life cycle depicted in Fig. 1 are given in the table below.



Model	Limit	u	e
SIS	$B\to\infty$, $\gamma=0$	0	
SIRS	$B\to\infty$	$\frac{2d}{\nu}$	$q_{I/I}-q_{I/R}$
SI	$\gamma = 0$	$\propto q_{O/I}$	$\frac{n-1}{n}q_{S/SI} - q_{S/I}$

(Frank, 1992; van Baalen & Sabelis, 1995; Gandon *et al.*, 2001). The precise evolutionary outcome depends on the interplay between within- and between-host selection, but, to our knowledge, only a couple of studies have considered how spatial structure may affect these predictions. First, Claessen & de Roos (1995) have shown that allowing for double infections in a spatial SIS model with no host demography leads to lower virulence relative to well-mixed populations. However, it is not clear whether this effect is due to selection at the within-host level or is more simply explained by an asymmetry in kin competition at the between-host level. Second, Caraco *et al.* (2006) investigated the effect of superinfection in a discrete-time spatially structured host–parasite interaction where the host population is not fixed. They found that, while maximal virulence was selected for in a well-mixed population, spatial structure selected for an intermediate level of virulence. Furthermore, coexistence of competing parasite strains was enhanced in space. Here again, this calls for further studies to elucidate the processes at work and better understand the interplay between within-host and between-host selection in spatially structured host–parasite interactions. In particular, localized transmission will in general affect the distribution of parasite strains both within and between hosts, and this can generate potential conflicts between the two levels of selection.

Experimental studies

Until recently, the interest in the evolution of spatially structured host–parasite interactions has mostly been driven by theoretical studies. Recent experimental studies have confirmed the general prediction that parasites should evolve more prudent strategies of host exploitation in viscous populations. Kerr *et al*. (2006) manipulated migration in an experimental metapopulation of bacteria (*E. coli*) and coliphage T4 embedded in a 96-well plate. They compared two treatments, a 'local migration' treatment, in which periodic transfers to neighbouring wells were performed, and a 'global migration treatment', in which transfers occurred with the same probability to any random well in the metapopulation. As predicted by the general theory, more rapacious phages were found to evolve in the 'global migration' treatment, while more prudent phages were favoured in the 'local migration' treatment.

A potential limitation of Kerr *et al*. (2006)'s protocole is that it does not directly manipulate the viscosity of the host population. Boots & Mealor (2007) circumvented this problem in a study of the evolution of parasite infectivity in a moth–virus interaction. By manipulating the viscosity of the food medium inhabited by moth larvae, they demonstrated that increased medium viscosity decreased larval dispersal and selected for lower parasite infectivity. A key result of this study is that infectivity responds nonlinearly to changes in viscosity: at intermediate viscosity of the medium, infectivity tended to evolve to higher levels. Although this effect was not statistically significant, it is reminiscent of some theoretical predictions (Kamo *et al.,* 2007; Lion & Boots, 2010). In a related study using the pathogenic bacteria *Pseudomonas aeruginosa*, Kümmerli *et al*. (2009) showed that increasing the viscosity of the growth medium led to lower dispersal and siderophore diffusion, and increased the fitness of siderophore producers, relative to siderophore-defective mutants. As siderophores are important virulence factors, this leads to the interpretation that higher population viscosity could lead to higher virulence. However, Kümmerli *et al*. (2009) implicitly restrict their attention to within-host competition, while the general theory of virulence evolution in spatially structured population focuses on between-host selection. The outcome of selection depends on the balance between the two levels of selection and, as the authors rightly note, on the exact biological mechanism by which virulence is triggered in the host.

The recent development of experimental tests of the spatial theory of virulence evolution paves the way for a fruitful cross-fertilization between theoretical and experimental studies. Although, up to now, experiments have validated the general message that population viscosity selects for more prudent strategies of host exploitation, the amount of data is still limited and calls for further studies in a variety of biological systems. Furthermore, theory suggests that the pattern can be more complicated depending on virulence mechanisms, trade-offs between parasite life-history traits, epidemiological characteristics of the disease (demographic turnover, long-lived immunity,...) and the topology of the contact network. This highlights the crucial importance of a detailed understanding of these factors in experimental or empirical studies.

Host evolution

The selection imposed by pathogens on their hosts has led to the evolution of various host defence strategies. In particular, a classical distinction is made between resistance mechanisms aiming to reduce the parasite load and the tolerance strategies that decrease the detrimental effects induced by the infection (Roy & Kirchner, 2000; Miller *et al.,* 2005; Råberg *et al.,* 2007; Little *et al.,* 2010). Yet, most theoretical studies on the evolution of host defence strategies have focused on well-mixed environments. These models have shown, in particular, how epidemiological dynamics feed-back on host evolution (Boots *et al.,* 2009). Spatial structure, however, may dramatically alter this evolution. Indeed, in a viscous environment, investing into your own defence against pathogens may also benefit your related neighbours as they become less likely to acquire an infection from yourself. Frank (1998b) and Schliekelman (2007) formalized this idea and showed that population viscosity may favour evolution towards higher levels of defence because spatial structure introduces an inclusive benefit of defence. Yet, those earlier models assume that the force of infection is constant and they lack the potential complexity emerging from epidemiological feedbacks. Spatially explicit models have been analysed under specific scenarios of host–parasite interactions (Brown & Hastings, 2003; Best *et al.,* 2011; Débarre *et al.,* 2012). In the following, we summarize these results and identify the forces acting on the evolution of various host defence strategies.

For simplicity, let us examine what happens when infected hosts can neither reproduce nor recover (which corresponds to the life cycle depicted in Fig. 1 with $\gamma = 0$). This assumption greatly simplifies the analysis because we no longer need to keep track of the change in mutant frequency in the infected hosts as their reproductive value is null (Best *et al.,* 2011; Berngruber *et al.,* 2013b). The change in the frequency f_H of a mutant host genotype is then given by

$$\frac{df_H}{dt} = f_H(1 - f_H)[\Delta B - \Delta D - \Delta H] \qquad (3)$$

The quantity ΔB is the difference between the reproduction rates of mutant and wild-type hosts. Similarly, ΔD is the difference between the death rates of uninfected mutant and wild-type hosts. The quantity ΔH is

the difference between the rates of infection experienced by the mutant and wild-type hosts.

It is clear that, in the absence of parasites, the infection risk vanishes (i.e. $\Delta H = 0$) and we recover the classical result that hosts evolve to maximize their net reproductive output (Charnov, 1976). In the presence of parasites, hosts must strike a balance between the net number of new uninfected hosts produced, $B-D$, and the number of susceptible hosts that are lost due to infection, $-H$. To make more progress at this stage, we need to specify the mechanisms and fitness costs of the defence strategy. For the sake of simplicity, we will start by analysing the evolution of defence strategies that limit the rate of infection and therefore tend to reduce the quantity ΔH in equation (3).

Lowering the rate of infection

The rate of infection experienced by a mutant host has the following expression:

$$H^* = \sigma^*(\beta[I|S^*] + \beta^*[I^*|S^*])$$

where σ^* is the mutant host's susceptibility to the disease. In the following, we analyse the evolution of three different defence strategies (Fig. 3) that the host can use to reduce the rate of infection. First, the host can decrease the susceptibility to the disease, σ^*, via an investment in various immunological or behavioural modifications (ρ_R). This corresponds to the classical definition of resistance (Roy & Kirchner, 2000; Best *et al.*, 2011). Second, the host can reduce the transmissibility of the pathogen, β^* (ρ_T). Third, any change in life-history trait leading to a reduction in the density of infected hosts experienced by a susceptible mutant host ($[I|S^*]$ and $[I^*|S^*]$) could, in principle, lead to a reduction in the rate of infection. For instance, an increased mortality upon infection (ρ_V) will lower the duration of the infection and could therefore lead to a lower local prevalence around uninfected mutant hosts. In this section, we study each of those three strategies (ρ_R, ρ_T and ρ_V) in turn. We further assume that defence has a cost that may reduce fecundity and/or survival. For the simulations, we use specific trade-offs between defence and fecundity introduced in earlier studies (Best *et al.*, 2011; Débarre *et al.*, 2012).

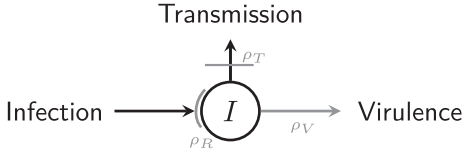


Fig. 3. Three possible strategies of host defence (see Section 3), symbolized in grey. For each type of defence strategy, the effect on the trait in a monomorphic host population is given. Classical resistance (ρ_R) and transmission-blocking resistance (ρ_T) decrease the baseline susceptibility (arbitrarily set to 1) and transmissibility (β_0), respectively. In contrast, altruistic suicide increases the baseline virulence (α_0) so that a higher investment into defence leads to an increased mortality upon infection.

For each defence strategy, ρ_i (with $i = R$, T or V), the selection gradient on the host can be expressed analytically by expanding equation (3) using the definitions in Box 1 and differentiating the term between square brackets with respect to the mutant host defence strategy, ρ_i^*. This allows us to find that a rare mutant host with a slightly higher investment into defence can invade if the quantity

$$\frac{\partial C}{\partial \rho_i^*} = \frac{\partial \text{cost}}{\partial \rho_i^*} + (1 - g_H)\frac{\partial \text{sat}}{\partial \rho_i^*} - (1 - g_P)\frac{\partial \text{prev}}{\partial \rho_i^*} \qquad (4)$$

is below a threshold. This quantity is the sum of different *fitness costs* associated with an increase in the allocation to defence:

1 the physiological cost of defence (how much defence decreases the host's fecundity or survival),

$$\partial\text{cost} = -[o|S]\partial b^* + \partial d^*,$$

2 the demographic cost of defence,

$$\partial\text{sat} = -b\partial q_{o/S^*},$$

quantified by a measure of habitat saturation (∂sat increases if defence reduces the local density of empty sites available for reproduction), minus:

3 the epidemiological benefit of defence,

$$\partial\text{prev} = \beta\partial(q_{I/S^*} + q_{I^*/S^*}),$$

quantified by a measure of local prevalence.

Importantly, the demographic cost of defence vanishes when host reproduction is fully global ($g_H = 1$), while the epidemiological benefit of defence is zero when parasite transmission is fully global ($g_P = 1$). Note, however, that the terms 'cost' and 'benefit' used above should not be taken too strictly: a strategy that would lower habitat saturation ($\partial\text{sat} < 0$), for instance, would represent a net benefit of defence.

A rare mutant host with a slightly higher investment into defence can evolve only if $\partial C/\partial \rho_i^*$ is below a threshold. We'll see below that this threshold depends on which life-history trait is affected by host defence. It is important to note that, for host evolution, the current state of theory does not allow for as much analytical insight as for the parasite. In particular, it is hard to compute the terms ∂sat and ∂prev, which represent marginal effects on the *local* densities of empty sites and infected hosts, respectively (in contrast, panels (b) and (c) of Figs 4–6 show the *global* host density and prevalence). Hence, we usually have to resort to a combination of unsolved

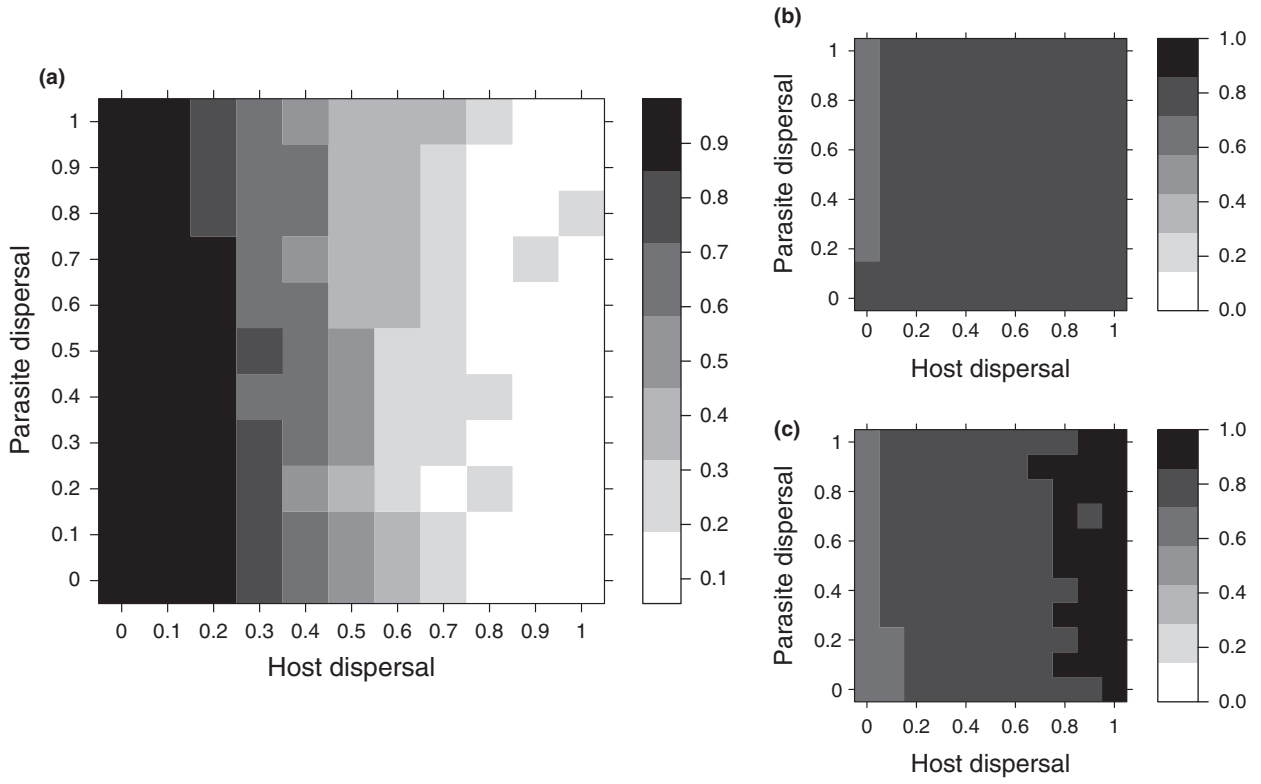


Fig. 4. Evolution of classical resistance, ρ_R. (a) Mean resistance. (b) Total host density, $p_S + p_I$. (c) Disease prevalence $p_I/(p_S + p_I)$. Stochastic simulations were run on a square lattice with the same parameters as in fig. 2a of Best *et al.* (2011): $b = 8$, $d = 0.1$, $\beta = 2$, $\alpha = 0.1$, $\gamma = 0$. See Best *et al.* (2011) for details on the trade-off between host fecundity and resistance. The simulations were initialized with 21 host strains with resistance between 0 and 1. Mutations between strains with adjacent values occurred at rate $\mu = 0.001$. For each combination of host and parasite dispersal rates, the mean value between $t = 750$ and $t = 1000$ was computed and averaged across 6 runs.

analytical expressions, numerical approximations and stochastic simulations (Débarre *et al.*, 2012). Nonetheless, it is still possible to discuss the effect of genetic and epidemiological spatial structuring on the evolution of host defence strategies.

Classical resistance: ρ_R

Classical resistance can be modelled as a decrease in host susceptibility to the disease: $\sigma = 1-\rho_R$ (Best *et al.*, 2011). Let us assume that hosts have no control on parasite transmissibility ($\beta^* = \beta$) and that other types of resistance are absent ($\rho_T = \rho_V = 0$). Then, a rare mutant host with a slightly higher resistance to the disease can invade if

$$\frac{H}{1-\rho_R} > \frac{\partial C}{\partial \rho_R^*} \tag{5}$$

where $\partial C/\partial \rho_R^*$ is given by equation (4). Equation (5) shows that the force of infection, H, must be sufficiently high to select for classical resistance. However, it is hard to disentangle the effects of host and parasite dispersal, as they potentially affect both sides of equation (5). Stochastic simulations provide a way to make progress. Figure 4 shows the outcome of simulations for various combinations of host and parasite dispersal. For convenience, we chose the same parameters as used by Best *et al.* (2011) in their Fig. 2a. Figure 4a shows that local host dispersal selects for higher resistance, whereas parasite dispersal has a negligible effect on the evolution of resistance. Given the relative impact of host and parasite migration in equation (4), this suggests that local parasite prevalence has a weak effect ($\partial \text{prev} \approx 0$) and that the main effect of spatial structure is through the term ∂sat. Indeed, a reduction in host fecundity due to higher resistance may lead to a higher local density of empty sites, thereby reducing competition for resources and resulting in a higher net reproductive output. This interpretation is indeed confirmed by a numerical examination of the magnitude of the different components of the gradient of selection (Débarre, 2014).

Transmission-blocking resistance: ρ_T

Transmission-blocking resistance is another way to lower the propagation of the parasite, but this strategy does not directly benefit the actor (who is already infected anyway). In a spatially structured population, however, a reduction in parasite transmissibility may

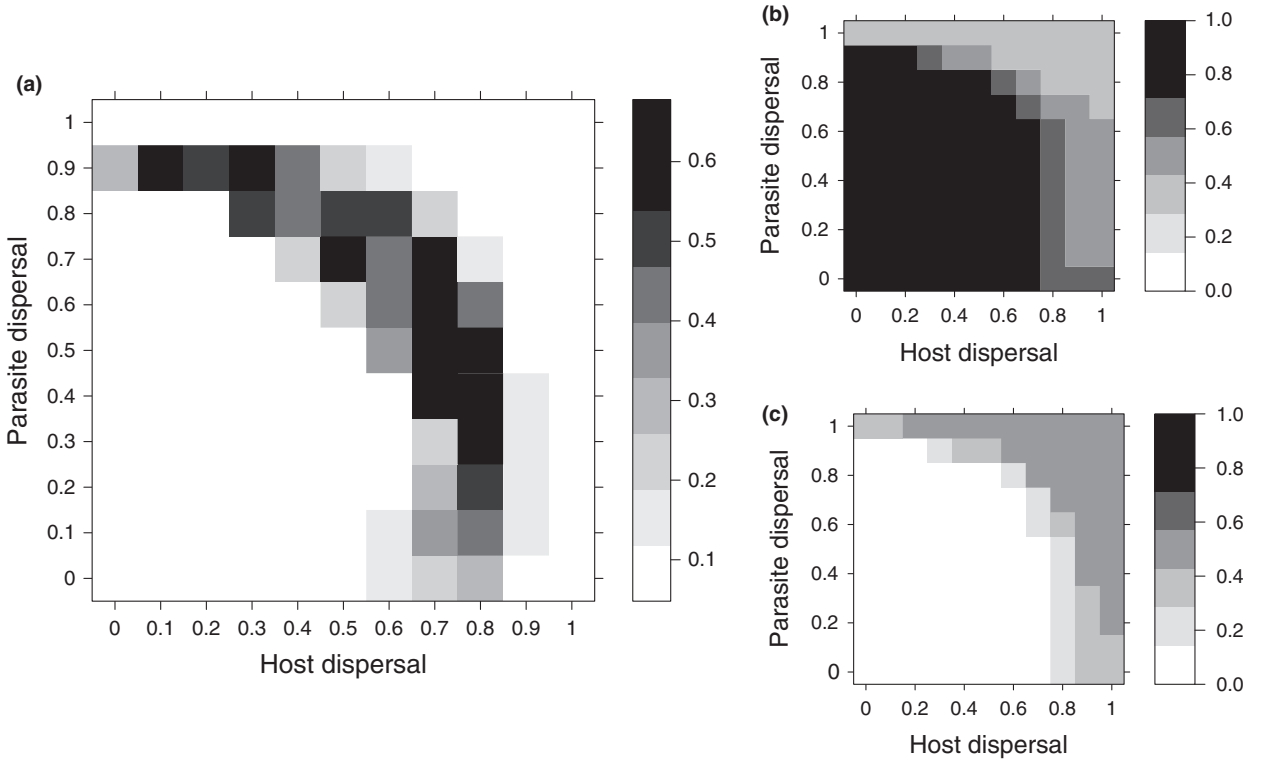


Fig. 5. Evolution of transmission-blocking resistance, ρ_T. (a) Mean resistance. (b) Total host density, $p_S + p_I$. (c) Disease prevalence $p_I/(p_S+p_I)$. Stochastic simulations were run on a square lattice with the same parameters as in fig. 4 of Débarre *et al.* (2012): $b = 5 - 0.1\rho_T^{1.2}$, $d = 1$, $\beta = 10$, $\alpha = 1$, $\gamma = 0$. The simulations were initialized with 21 host strains with resistance between 0 and 1. Mutations between strains with adjacent values occurred at rate $\mu = 0.005$. For each combination of host and parasite dispersal rates, the mean value between $t = 4750$ and $t = 5000$ was computed and averaged across 6 runs.

benefit the actor's neighbour and thus evolve through inclusive fitness benefits. Assuming that other types of resistance are absent ($\rho_R = \rho_V = 0$) transmission-blocking resistance evolves if:

$$(1 - g_P) r_{I^*S^*} > \frac{\partial C}{\partial \rho_T^*} \tag{6}$$

where $r_{I^*S^*} = q_{I^*/S^*} - q_{I^*/S}$ is the interclass relatedness. In a well-mixed population, relatedness vanishes and, as expected, reduced transmissibility cannot evolve if this host defence strategy has direct fitness costs (i.e. if $\partial C = \partial \text{cost} < 0$). In contrast, in spatially structured populations, this relatedness can be high because infected hosts near a mutant susceptible host tend to also bear the mutation, because of limited dispersal. Reduced transmissibility may thus evolve in spatially structured environments when this mutation benefits a related uninfected individual.

Stochastic simulations can be used to explore the influence of host and parasite dispersal on the evolutionary outcome (Fig. 5). As expected, reduced transmissibility only evolves if both host and parasite dispersal rates are nonzero, otherwise the LHS of (6) vanishes. Interestingly, when either host or parasite dispersal is too local, disease extinction may occur (Fig. 5c). Of course, after parasite extinction, selection for host defence disappears and the cost of defence selects against transmission-blocking resistance. This epidemiological feedback explains the nonmonotical effect of dispersal on the evolution of host: transmission-blocking resistance is maximized for intermediate dispersal rates of both the host and the parasite. Note that a similar result was found in a slightly different model by Horns & Hood (2012): the authors compared the invasion success of a transmission-blocking host genotype (which they call 'resistant') versus a 'tolerant' host that does not block transmission and found that transmission-blocking strategies was favoured under limited dispersal.

Altruistic suicide resistance: ρ_V

Altruistic suicide is another defence strategy that does not provide direct benefits to the actor. Our model allows us to capture the effects of spatial structure on the evolution of this strategy. Assuming that the other types of resistance are absent ($\rho_R = \rho_T = 0$) altruistic suicide defence evolves if:

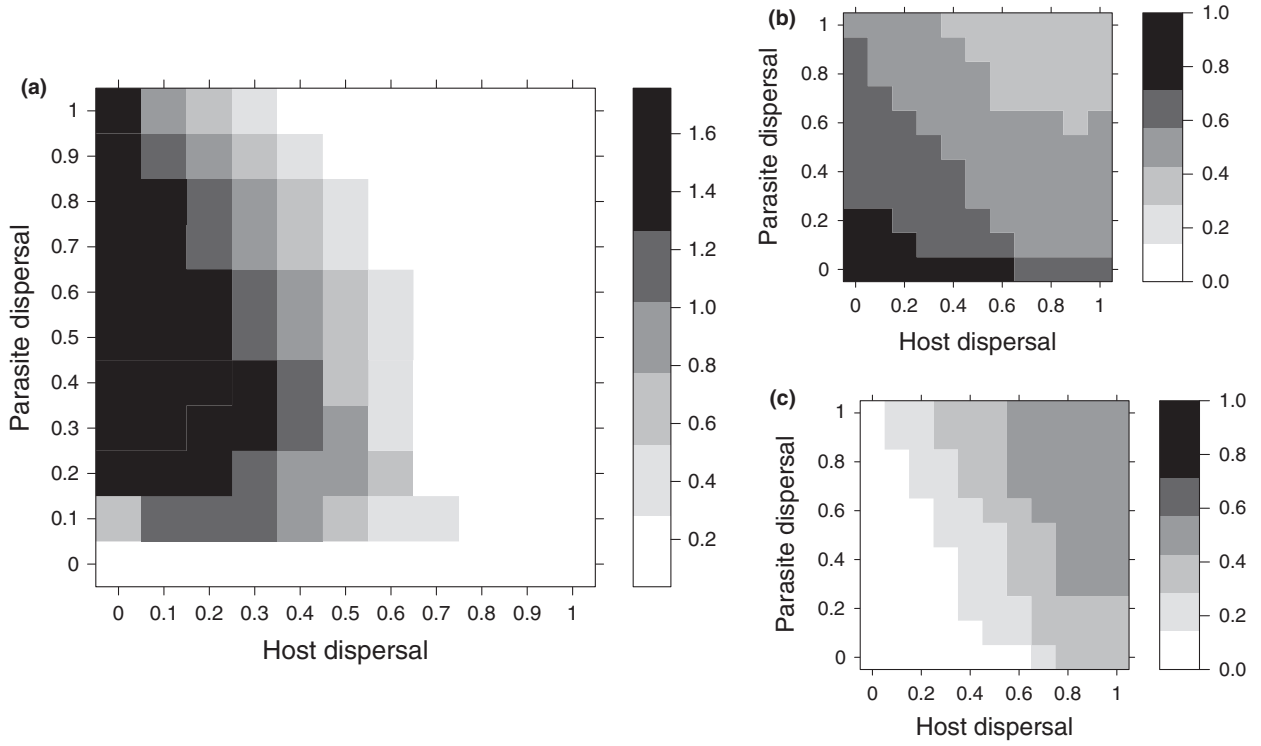


Fig. 6. Evolution of altruistic suicide resistance, ρ_S. (a) Mean resistance. (b) Total host density, $p_S + p_I$. (c) Disease prevalence $p_I/(p_S + p_I)$. Stochastic simulations were run on a square lattice with the same parameters as in fig. 3 of Débarre *et al.* (2012): $b = 5 - 0.1\rho_V^{1.2}$, $d = 1$, $\beta = 10$, $\alpha = 1 + \rho_V$, $\gamma = 0$. The simulations were initialized with 21 host strains with resistance between 0 and 2. Mutations between strains with adjacent values occurred at rate $\mu = 0.001$. For each combination of host and parasite dispersal rates, the mean value between $t = 750$ and $t = 1000$ was computed and averaged across 6 runs.

$$0 > \frac{\partial C}{\rho_V^*} \tag{7}$$

Condition (7) may be used to understand how spatial structure (i.e. limited host and parasite dispersal) may act on the inclusive fitness of the host (see also Débarre *et al.* (2012), Berngruber *et al.* (2013b)). First, this form of resistance is associated with death of related neighbours (when they are infected) and creates empty spaces around the actor ($\partial\text{sat} < 0$). Second, this form of resistance limits the local density of infected hosts ($\partial\text{prev} < 0$). Figure 6 shows that selection for altruistic suicide is maximized at low host dispersal and at intermediate parasite dispersal. The monotonical effect of host dispersal is clearly due to the build-up of genetic structure in the host with higher viscosity. The non-monotonical effect of parasite dispersal results from a balance between two effects. When parasite dispersal is very high, there is no spatial structure and the RHS of (7) is driven by the direct cost of host defence. When parasite dispersal is too low, however, the prevalence of the disease decreases (see Fig. 6c) and this limits the benefits of an investment into host defence. Indeed, as for transmission-blocking resistance (Fig. 5), the evolution of altruistic suicide is maximized at intermediate parasite dispersal. Very similar results were obtained in a model describing the interaction between lytic phages and their bacteria (Fukuyo *et al.*, 2012; Berngruber *et al.*, 2013b): if parasite migration is too low, the parasite epidemic does not take off and this limits the benefit of host resistance (Berngruber *et al.*, 2013b).

Other defence strategies

In the above section, we focused on various defence strategies that may act via a reduction of the rate of infection. The evolutionary response of the host could also take other routes.

For instance, it is possible that, in the presence of parasites, the host's optimal reproductive effort differs from the evolutionarily stable allocation between fecundity and survival in an uninfected population. In the absence of parasites, the evolution of reproductive effort is governed by the shape of the trade-off between the different life-history traits affected by reproductive effort. Spatial structure has been found to select for higher or lower reproductive effort compared with well-mixed populations, depending on the life cycle.

This is driven by kin competition (Pen, 2000; Lion, 2010). Not surprisingly, adding parasites introduces higher levels of complexities. Although the evolution of increased reproductive effort in response to parasitism has received little attention in a spatial context, it is clear that it is a potential tolerance strategy for the host, that is a strategy by which the host mitigates the detrimental effects of the disease without fighting the infection (Roy & Kirchner, 2000; Råberg *et al.,* 2007; Boots, 2008). More surprising is the finding that increased background mortality or senescence can also evolve in spatially structured host populations, provided the overall infection rate is very high (Mitteldorf & Pepper, 2009; Débarre *et al.,* 2012). This effect is solely mediated by changes in local epidemiological and demographic structure (the ∂sat and ∂prev terms in equation (4)).

It would be particularly interesting to expand the present framework to study the evolution of communication among hosts to signal the presence of a pathogen or a predator. There is a growing number of studies reporting the existence of plant to plant airborne signalling (Vet & Dicke, 1992; Bruin *et al.,* 1995; Heil & Karban, 2010). If the production of the signal is costly, it is very likely that the evolution of this trait is going to depend on the relatedness between the emitter and the receiver of the signal. Hence, higher spatial structure may favour the evolution of warning signals among hosts (Kobayashi & Yamamura, 2007). In some other biological systems, the communication may involve a third species that may interact with the pathogen or the predator (Sabelis *et al.,* 2011). Taking into account the effect of spatial structure on the coevolution between two species to fight a third one raises new theoretical challenges (Sabelis *et al.,* 2002).

It is important to bear in mind that the predictions given above are based on the simplified assumption that infected hosts can neither reproduce nor recover. If this assumption does not hold, additional selective pressures need to be accounted for and this may lead to different conclusions (Débarre *et al.,* 2012). For instance, the evolution of altruistic suicide becomes more difficult when infected hosts are allowed to reproduce and/or to recover (Débarre *et al.,* 2012). Besides, more complex life cycles allow us to consider the evolution of a whole range of other defence strategies (i.e. clearance, modified reproductive effort of infected hosts). This may shed a new light on the classical distinction between resistance and tolerance. Spatial structure has been shown to limit the spread of a tolerance trait such as reduced virulence (Débarre *et al.,* 2012). The reason is that mutants with a reduced virulence live longer and therefore free up fewer empty sites and have a longer infectious period. Hence, the direct beneficial effect of reduced virulence is counterbalanced by detrimental indirect effects. This example shows that, in spatially structured host–parasite interactions, the distinction between resistance and tolerance can be blurry. Increasing fecundity or survival may alter the local epidemiological structure and therefore the risk of infection. Thus, what is defined as a tolerance trait in a well-mixed population may appear as a resistance trait in a spatially structured population, because of indirect fitness effects. Indeed, altruistic suicide may be viewed as an antitolerance trait.

Some empirical and experimental tests

Experimental studies investigating the impact of spatial structure on the evolution of host defence strategies remain scarce and usually focus on 'classical' resistance (see Fig. 3). For instance, Thrall & Antonovics (1995), Carlsson-Granér & Thrall (2002) combined simulation models and longitudinal studies to reveal the importance of the connectivity of the environment on host resistance evolution. More connectivity is described as a higher density of host populations and yields higher equilibrium frequency of resistance (Carlsson-Granér & Thrall, 2002; Jousimo *et al.,* 2014). It is difficult, however, to discuss these results in the light of our simple model as the notion of connectivity is different from our measures of dispersal. It would be particularly interesting to extend our analysis to study the effect of host fragmentation (by allowing a fraction of the host sites to be unsuitable as in Carlsson-Granér & Thrall (2002)) on the evolution of host resistance.

In Débarre *et al.* (2012), we discussed several empirical examples not only in insects (aphids, ants and bees) but also in humans that illustrate how very different host defence strategies may have beneficial effects on neighbouring conspecifics. We argued that spatial structure was a key factor in the evolution of these host defence strategies. A similar conclusion is reached in a recent theoretical study investigating the evolution of 'slave rebellion' in ant species suffering from slavemaking ants (Pamminger *et al.,* 2014). Interestingly, three recent studies have used experimental evolution to further explore and demonstrate the effect of spatial structure on the evolution of altruistic suicide in bacteria. Fukuyo *et al.* (2012) used an artificially engineered suicide mechanism in *E. coli*. Upon infection by phage λ the altruistic bacteria carrying this suicide mechanism triggers the bacterial genome degradation and leads to the death of both the host and the virus. Fukuyo *et al.* (2012) competed altruistic bacteria against wild-type bacteria in the presence or in the absence of the phage λ. As expected by theory they showed that altruistic suicide has a selective benefit in a spatially structured environment (soft agar) but not in a well-mixed environment (liquid).

Similar results have been obtained with naturally occurring suicide strategies in bacteria. Many abortive

infection systems (Abi) have evolved and respond to phage attacks by causing infected cells to die together with the infecting phage (Chopin *et al.,* 2005; Labrie *et al.,* 2010). Berngruber *et al*. (2013b) studied the effect of spatial structure on the evolution of the gene *Lit* found in many genomes of *E. coli* K12 strains where it is part of the defective prophage e14 (Kao & Snyder, 1988; Linder *et al.,* 1994). In the absence of phage infection, the Lit protein is produced and accumulates in an inactive form. Infection by T-even phages (T2, T4 or T6) triggers the activation of the Lit protein which acts as a protease that cleaves the ribosomal translation elongation factor Tu (RF-Tu) (Yu & Snyder, 1994; Georgiou *et al.,* 1998). Cleavage of EF-Tu leads to the immediate arrest of translation and ultimately to cell death before the phage can complete its replicative cycle. The competition between bacteria with or without the Lit mechanism in the presence or in the absence of T4 phages allowed studying how spatial structure affects the evolution of altruistic suicide. Unlike Fukuyo *et al*. (2012) who contrasted evolutionary outcomes in two extreme environments (agar plates versus liquid cultures), this study varied the amount of mixing more continuously. Different levels of mixing were obtained with the use of small sterile stainless beads allowed to move randomly on the agar plates for different amounts of time. This experimental set-up confirmed the importance of spatial structure for the evolution of altruistic suicide, but it also demonstrated that too little mixing may prevent the evolution of altruistic resistance. Indeed, as expected from the theory, resistance evolution is maximized for intermediate mixing rates of the parasite because low mixing prevents the spread of the epidemic. These results were confirmed with another experimental system study (Refardt *et al.,* 2013). This study focuses on the evolution of yet another naturally occurring altruistic suicide mechanism which is coded by the Rex abortive infection system carried by phage λ. This systems codes for an intracellular sensor (RexA) that is activated when the bacterial cell hosting phage λ is infected by a lytic phage T4rII. The activation of RexA leads to the activation of RexB, a membrane-anchored ion channel, which leads to a drop of a membrane potential and to the death of the bacterium. Again, competition between bacteria carrying or not the Rex Abi system highlighted the importance of spatial structure for the evolution of altruistic suicide. In this study, the amount of mixing was manipulated with varying levels of agarose in the culture. This study also showed that the fitness of the Abi system was maximized for intermediate levels of mixing. Taken together, these different studies demonstrate the importance of spatial structure on the evolution of resistance. But, they also raise new questions. For instance, it is still unclear how this altruistic defence strategy can outcompete seemingly simpler and more classical defence strategies preventing infection in the first place. The fact that many naturally occurring Abi are often carried by prophages suggests that the horizontal transfer of these defence strategies may play an important role in their evolutionary success.

Coevolutions

Coevolution within species

Before discussing the possible coevolution going on between pathogens and their hosts, it is important to recognize the possibility that space may also affect the coevolution between several life-history traits. In the pathogen, for example, virulence is often assumed to be genetically correlated with transmission (Alizon *et al.,* 2009). But, even in the absence of genetic constraints, one may expect both traits to respond to an increase in spatial structure. Interestingly, van Baalen & Boerlijst (2006) have shown that space could lead to the emergence of a trade-off between transmission and the duration of the infection in a model with local recurrent outbreaks. This is due to selection for higher frequency of epidemics (a selection force that vanishes in the absence of spatial structure).

In the host, the coevolution between different types of defence strategies has often been considered in well-mixed environments (Restif & Koella, 2004; Miller *et al.,* 2007; Garnier *et al.,* 2012). Yet, the potential effect of spatial structure on this coevolution remains overlooked (but see Berngruber *et al*. (2013b)). Studying the coevolution between host mobility and host resistance would also be particularly interesting (see Le Galliard *et al*. (2005) on the coevolution between mobility and altruism). More generally, studying how space could mould the allocation towards different life-history traits in each interacting species is important to understand and predict syndromes associated with different degrees of viscosity of the environment.

Coevolution between species

The theoretical study of the coevolution between host and parasite traits in space is heavily biased towards models with very strong assumptions regarding the pattern of genotype by genotype (G×G) interactions and do not consider the possibility of life-history evolution (Frank, 1991; Gandon *et al.,* 1996; Burdon & Thrall, 1999). Besides, these studies often assume that host and parasite population sizes are fixed and thus do not fit squarely within the framework developed above where epidemiology is coupled with evolution. Yet, theses studies have been very useful to demonstrate the impact of spatial structure on the coevolutionary dynamics. In particular, these approaches have been used extensively to examine the impact of host and

parasite dispersal on the maintenance of genetic diversity in both species. Thrall & Burdon (2002) showed that, in a classical gene-for-gene model of coevolution, the highest levels of polymorphism were reached at lower migration rates among populations. They also showed how increasing pathogen migration rates could select for generalist strategies where the pathogen can infect a broader range of resistant hosts (by accumulating 'virulent' alleles, that is alleles that can escape recognition by 'resistant' plants). Other models of coevolution showed that higher host and parasite migration rates could lead to the synchronization of coevolutionary dynamics and, as a consequence, to the loss of spatial structure (Gandon *et al.*, 1996; Nuismer *et al.*, 2000; Gavrilets & Michalakis, 2008). Limited gene flow among populations may thus be a way to maintain a very large amount of genetic diversity in the host and the pathogen metapopulations (Frank, 1991). When populations are relatively isolated, migration may be a way to reintroduce new adaptive variation and to fuel the coevolutionary process. In fact, this is why these models show that the amount of local adaptation of the parasite is driven by the ratio between host and parasite migration rates. Parasites are expected to be locally adapted only when they migrate more than their hosts (Gandon *et al.*, 1996; Gandon, 2002). Importantly, this prediction was obtained using a specific host–parasite Lotka–Volterra interaction, where dead hosts are directly converted into new parasites, much like in a predator–prey interaction.

To reconcile these results with the more traditional epidemiological framework used in the previous sections, we modified our baseline model (Fig. 1) to allow for matching-allele coevolution between the host and the parasite. Two host types and two parasite strains are considered. Under the assumptions of the matching-allele model, the type-1 (resp. 2) parasites can only infect type-1 (resp. 2) hosts. We track the global and local densities of susceptible hosts of type 1 (S_1) and 2 (S_2), and hosts infected by parasites of type 1 (I_1) and 2 (I_2), respectively. In this particular model, hosts infected by parasite i necessarily bear host genotype i. We then compute the local adaptation of parasites using the following definition:

$$\mathrm{LA} = \frac{1}{2}\left[\left(p_{S_1 I_1} - p_{S_1} p_{I_1}\right) + \left(p_{S_2 I_2} - p_{S_2} p_{I_2}\right)\right]$$

which is simply the spatial covariance between host and parasite genotypes at the scale of neighbouring sites (Nuismer & Gandon, 2008). Our stochastic simulations confirm earlier predictions that parasites are locally adapted to their host when $g_P > g_H$ (Fig. 7a). Furthermore, we show that when parasites are more locally adapted to their host, host density declines (Fig. 7b), as expected. Parasite prevalence is minimal when the host is locally adapted (i.e. when $g_H > g_P$) but parasite local adaptation does not yield maximal prevalence. Maximal prevalence is reached when both the host and the parasite have large migration rates (Fig. 7c). Recently, Ashby *et al.* (2014) studied host–parasite coevolution in another spatially explicit model. In this study, the specificity is governed by a gene-for-gene model of interaction where host resistance and pathogen infectivity are associated with constitutive fitness costs. They found that generalist host strategies (i.e. accumulation of a larger number of resistance genes) could evolve more readily in spatially structured environments. It is worth noting the similarity with the effect of spatial structure on classical resistance (see Section 3). It would be interesting to explore the relative effects of host and parasite dispersal rates on the evolution of host generalism to see whether we recover the same pattern as in Fig. 3. It would also be enlightening to study the relative impact of host and parasite migration rates on patterns of local adaptation under this model of specificity to explore the robustness of the results presented in Fig. 7.

The study of life-history coevolution between pathogens and their host remains very limited. Best *et al.* (2011) studied numerically the coevolution between pathogen virulence and host resistance. They found that lower mixing selects for higher resistance and lower pathogen virulence. Yet, it would be interesting to study the effects of host and parasite migration rates independently on this equilibrium. It is unclear whether similar coevolutionary outcomes would be reached if other defence mechanisms were considered (e.g. tolerance, altruistic resistance). Another scenario to consider would be the coevolution between recovery rates and virulence. In a well-mixed environment, van Baalen (1998) showed that coevolution may lead to evolutionary bistabilty. In other words, depending on the initial density the system could either evolve towards a relatively pacific equilibrium (no investment in immunity and low virulence) or towards a more aggressive equilibrium (high investment in immunity and high virulence). In a spatially structured environment, different populations may thus reach different equilibria. This scenario would be analogous to models of adaptation in heterogeneous environments with two habitats (Ronce & Kirkpatrick, 2001; Débarre *et al.*, 2013). Each habitat may be characterized by its own optimal phenotype and migration from the other habitat would introduce maladaptive genotypes. These models take explicitly into account the feed-back between demography and evolution. Hence, there are very tight connections between these models of adaptation in heterogeneous environments and the spatial evolutionary epidemiology framework discussed above.

Empirical and experimental studies

Experimental and empirical studies of coevolution are also biased towards the study of the ability of the

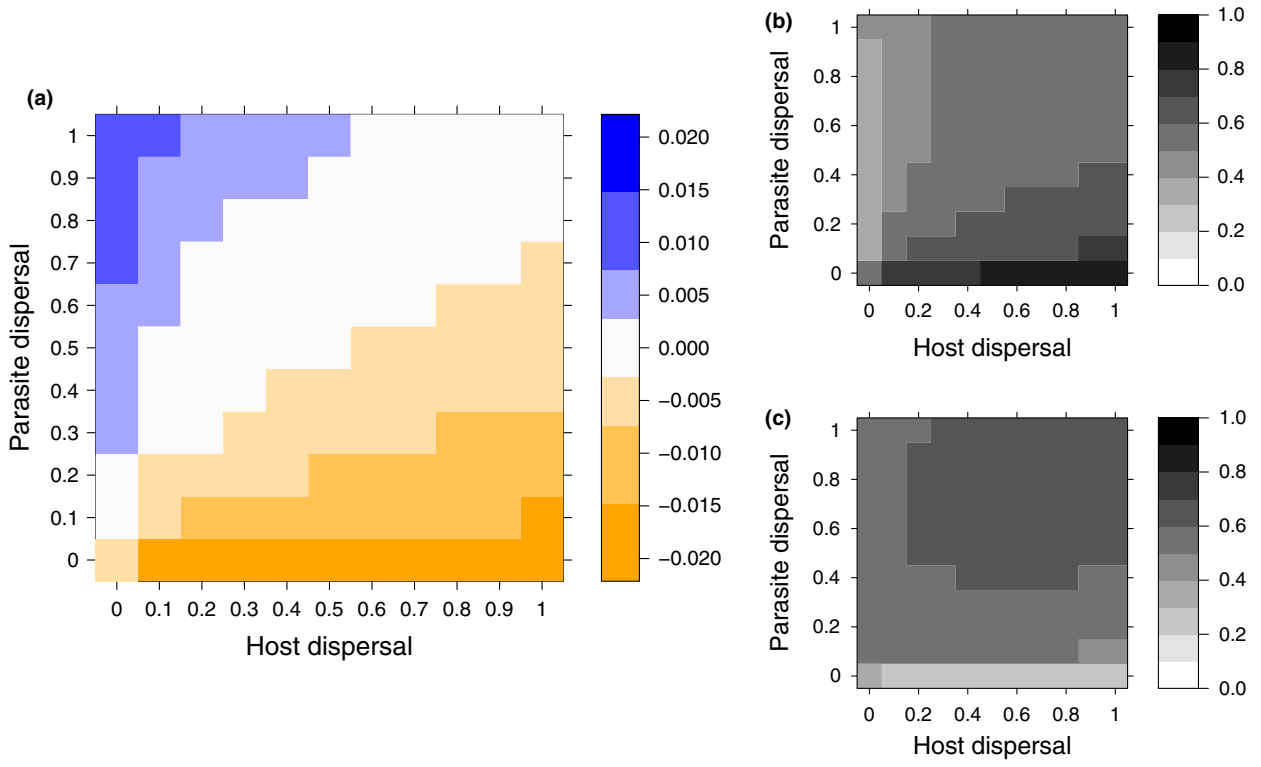


Fig. 7. Coevolution and local adaptation. (a) Mean local adaptation. (b) Total host density, $p_S + p_I$. (c) Disease prevalence $p_I/(p_S + p_I)$. Stochastic simulations were run on a square lattice with parameters: $b = 1$, $d = 0.1$, $\beta = 2$, $\alpha = 0.1$. Simulations were run with two host strains and two parasite strains following a matching-allele model. Local adaptation was measured as $LA = ((p_{S_1I_1} - p_{S_1}p_{I_1}) + (p_{S_2I_2} - p_{S_2}p_{I_2}))/2$. For each combination of host and parasite dispersal rates, the mean value between $t = 750$ and $t = 1000$ was computed and averaged across 6 runs.

parasite to infect and the ability of the host to prevent this infection. This is probably because this all-or-nothing (qualitative) response is easier to monitor than more quantitative measures of life-history traits. Besides, there is often an unambiguous link between the ability to infect and host and parasite fitness. Measuring infectivity thus provides an easy way to estimate the mean fitness of the parasite and of the host [but see Lemoine *et al.* (2012)]. In addition, transplant experiments among different locations also provide a way to estimate patterns of local adaptation (Kawecki & Ebert, 2004; Blanquart *et al.*, 2013; Brockhurst & Koskella, 2013). Transplant experiments on many different biological systems tend to confirm that the ratio of host and parasite migration rates is key in the emergence of parasite local adaptation (Greischar & Koskella, 2007; Hoeksema & Forde, 2008). Some experimental studies on bacteria and phage further confirm this theoretical prediction (Morgan *et al.*, 2005). More generally, empirical studies confirm the importance of spatial structure to understand the complex patterns emerging from coevolutionary dynamics (Ebert, 1994; Thompson, 1994, 2005; Laine, 2005; Koskella, 2014). Besides, these studies often reveal the complexity of the hierarchical spatial structure occurring in wild populations (Laine, 2005; Koskella *et al.*, 2011; Koskella, 2013; Tack *et al.*, 2014). Taking into account this hierarchical structure as well as other forms of heterogeneity of the habitat (e.g. unsuitability of some sites) represents a difficult but interesting theoretical challenge.

Relatively, few studies provide more quantitative measures of host and parasite life-history traits. Ebert (1994) found evidence that sympatric combination of host and parasite are characterized by higher spore load and stronger deleterious effects on both survival and fecundity. But, the lack of theoretical predictions regarding the effect of spatial structure on the coevolution of host and parasite life-history traits does not help to make sense of this pattern. Thrall & Burdon (2004) working on a wild plant–pathogen system obtained quantitative measures of pathogen performance. They found strong evidence of the existence of a cost in within-host growth rate associated with the ability of the pathogen to grow on resistant hosts. This indicates that there might be a trade-off between the aggressivity of the pathogen (spore production) and its ability to

infect many different hosts. Similarly, from the host side, several studies found evidence that resistance to pathogens may be associated with fitness costs in various species (Kraaijeveld & Godfray, 1997; Burdon & Thrall, 2003; Tian *et al.,* 2003). Yet, fitness costs are measured on a few fitness-associated traits and a complete description of the effects of resistance on the whole life cycle is often lacking. Further studies at the interface between the 'gene-for-gene' (i.e. qualitative) and the 'life-history' (i.e. quantitative) views of coevolution are needed to try link these two different perspectives.

Perspectives

The emergence of a theoretical framework incorporating the effects of epidemiology and evolution in spatially structured environments provides a deeper ecological understanding of host–parasite evolution. It also helps connect the field of host–parasite interactions to the broader context of theoretical evolutionary biology. This is particularly insightful as it sheds light on major evolutionary forces identified in other parts of the field: kin selection, genetic drift and migration.

The present framework needs to be extended to incorporate a wider diversity of host and parasite life cycles. We already know that the evolution of parasite virulence and the evolution of host resistance mechanism can be very sensitive to the specificities of the assumed life cycles (Lion & Boots, 2010; Débarre *et al.,* 2012). The robustness of the results discussed in this study remains to be investigated for more complex epidemiological models (e.g. with vertical transmission, multiple infections, age structure…).

It is important to note that the present framework is limited by its focus on equilibrium states. The results reviewed above rely on classical assumptions of Adaptive Dynamics (Geritz *et al.,* 1998): mutations are assumed to be rare, and this allows for a decoupling of epidemiological and evolutionary dynamics. In many epidemic situations, however, the host–parasite population is far from equilibrium and the high mutation rates of some pathogens (e.g. RNA viruses) fuel the rapid evolution of virulence and other pathogen traits. The prediction of the joint epidemiological and evolutionary dynamics has been developed in well-mixed environments (Day & Proulx, 2004; Day & Gandon, 2006; Berngruber *et al.,* 2013a). It would be particularly interesting to extend this to spatially structured environments. For instance, this could help describe transient selective pressures acting at the front of an invading epidemic. In addition, understanding transient evolutionary dynamics may also be particularly helpul to public health management. In particular, several attempts have been made to better understand the spread of drug resistance in spatially heterogeneous environments (Débarre *et al.,* 2009). Generalizing those studies to a broader range of epidemiological scenarios would help identify strategies that limit or even prevent the spread of drug resistance in spatially structured environments.

The analysis of the effects of spatial structure on different components of host–parasite interactions is calling for more experimental and empirical studies to validate theoretical predictions. Microbial systems are particularly well suited to explore the effects of spatial structure because the amount of mixing can be experimentally manipulated. It may, however, be difficult to generalize from the study of a handful of experimental evolution studies on bacteriophages. More experimental studies on a diverse range of organisms are needed. In addition, the development of new ways to analyse the dynamics of infectious diseases may yield novel techniques to monitor the spatial spread and the evolution of pathogens (Biek *et al.,* 2007; Pybus *et al.,* 2012). Ultimately, this confrontation between theoretical predictions, experimental tests and empirical studies will provide a better understanding of spatially structured host–parasite interactions.

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