Evolution of Host Life-History Traits in a Spatially Structured Host-Parasite System

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abstract: Most models for the evolution of host defense against parasites assume that host populations are not spatially structured. Yet local interactions and limited dispersal can strongly affect the evolutionary outcome, because they significantly alter epidemiological feedbacks and the spatial genetic structuring of the host and pathogen populations. We provide a general framework to study the evolution of a number of host life-history traits in a spatially structured host population infected by a horizontally transmitted parasite. Our analysis teases apart the selective pressures on hosts and helps disentangle the direct fitness effect of mutations and their indirect effects via the influence of spatial structure on the genetic, demographic, and epidemiological structure of the host population. We then illustrate the evolutionary consequences of spatial structure by focusing on the evolution of two host defense strategies against parasitism: suicide upon infection and reduced transmission. Because they bring no direct fitness benefit, these strategies are counterselected or selectively neutral in a nonspatial setting, but we show that they can be selected for in a spatially structured environment. Our study thus sheds light on the evolution of altruistic defense mechanisms that have been observed in various biological systems.

Keywords: host defense, evolutionary epidemiology, spatial structure, tolerance, resistance, kin selection, altruism, suicide.

Introduction

Parasites are ubiquitous and impose important selective pressures on their hosts. There is overwhelming evidence that hosts can evolve to respond to these selective pressures. In humans, for instance, since the discovery of the protecting effect of sickle-cell heterozygosity against malaria (Allison 1954; Lederberg 1999), several other genes involved in susceptibility to pathogens have been discovered (Hill and Motulsky 1999). More generally, selection imposed by pathogens on their hosts has led to the evolution of various host defense mechanisms, ranging from target-site mutations to immunological or behavioral modifications. The distinction between resistance and tolerance is a common way to classify this diversity of host defense strategies (Roy and Kirchner 2000; Råberg et al. 2007; Boots 2008). Resistance mechanisms consist of fighting directly against the parasite, either through avoidance (i.e., reducing the chance of getting infected) or through increased recovery (i.e., rapidly clearing the infection). On the other hand, tolerance mechanisms consist of mitigating the detrimental effects that parasites have on their hosts after infection. This can happen through reducing the additional mortality due to the infection (the parasite's virulence) or through restoring the fecundity of infected hosts. Because resistance and tolerance alter the dynamics of parasites differently, epidemiological feedbacks are also expected to differ, influencing in turn the evolutionary outcomes (Boots et al. 2009). It is therefore important to understand how epidemiological feedbacks affect the evolution of host defense, and there are indeed a growing number of theoretical studies devoted to this topic (reviewed in Boots et al. 2009).

Space and population viscosity have been shown to have a great influence on the evolution of traits such as dispersal (Hamilton and May 1977; Ferrière and Le Galliard 2001; Ronce 2007), altruism (see Lehmann and Keller 2006; Lehmann and Rousset 2010 for reviews), and parasite virulence (see, e.g., Boots and Sasaki 1999; Lion and Boots 2010). Yet most studies on the evolution of host defense consider unstructured environments (i.e., well-mixed environments without spatial structure; see, for instance, Gillespie 1975; Antonovics and Thrall 1994; van Baalen 1998;

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Gandon et al. 2002; Restif and Koella 2004; Best et al. 2009). Only a few studies have investigated the influence of spatial structure on host evolution (Frank 1998; Brown and Hastings 2003; Schliekelman 2007; Best et al. 2011). Frank (1998) showed that investment in the induction of defense—which in his model corresponds to avoidance, that is, reduced host susceptibility—is favored when relatedness is high. In Frank's model, however, the probability of attack is a fixed quantity: potential epidemiological feedbacks are ignored. Similarly, Schliekelman (2007) showed that family structure could affect the evolution of host defense, but again, epidemiological feedbacks were neglected. Still, these two studies show that spatial structure can influence the evolution of host defense. Brown and Hastings (2003) considered the evolution of host resistance with a spatially explicit model for the specific case where the evolving host shares a pathogen with a superior competitor. They found that spatial structure could lead to lower levels of resistance, because this allows the host to use the disease as a weapon against its competitor. This conclusion, of course, requires the presence of a competitor that shares the same natural enemies. Finally, epidemiological feedbacks were taken into account in a recent study by Best et al. (2011) on the influence of spatial structure on the evolution of host defense. These authors investigated the evolution of host avoidance—that is, reduced susceptibility—under a range of mixing patterns, from fully local to fully global. Assuming that the parasites castrate their hosts and cannot be cleared (i.e., that recovery is not possible), they found that local interactions favored the evolution of host avoidance.

In this article, we extend these studies by investigating how spatial structure alters the evolution of various host defense strategies. Using spatial moment equations (van Baalen 1998, 2002; Rand 1999), we first derive a general expression for the gradient of selection, which helps disentangle the different effects of the spatial structure in terms of genetic, demographic, and epidemiological structuring. The derivation of this gradient of selection does not involve moment-closure approximations: the result is a general expression that allows the identification of the different mechanisms contributing to the selection pressure. We then focus on the evolution of two types of host defense: reduced disease transmission and suicide upon infection, strategies that are counterselected in a nonspatial setting. We use an approximation of spatial structure—the pair approximation (Matsuda et al. 1992)—to numerically estimate some of the terms of the selection gradient. Finally, we confirm our results with stochastic, individual-based, and spatially explicit simulations. Our partitioning of the effects of spatial structure into genetic, demographic, and epidemiological components reveals that the reasons why spatial structure promotes the evolution of reduced disease transmission differ from the reasons why it promotes suicide upon infection. Finally, we discuss how our results help us understand some seemingly altruistic defense mechanisms observed in nature, from systems allowing for the "suicide" of bacteria infected by phages to aphids releasing cornicle secretions upon attack by parasitoids.

Epidemiological Model

We model a population of asexually reproducing hosts living on a network of sites. Each site can be either empty (○) or occupied by one susceptible (S) or infected (I) individual. Following Boots and Sasaki (1999) and Best et al. (2011), we assume that interactions (reproduction, transmission) can be either local or global.

In the absence of infection, only two types of events affect individuals: death and reproduction. Death occurs at a constant rate d. At rate b_S, individuals produce offspring that can disperse either globally to a random empty site (with probability g_R) or locally to an empty neighboring site (with probability $1 - g_R$). The average per capita reproduction rate is therefore $b_S[g_R p_\circ + (1 - g_R)q_{\circ|S}]$, where $q_{\circ|S}$ is the average density of empty sites in the neighborhood of a susceptible individual and $p_\circ$ is the global density of empty sites.

In the presence of parasites, the fecundity of infected hosts b_I may be lower than the fecundity of susceptible hosts ($b_I \leq b_S$), and the infected hosts may suffer from an increased mortality because of the parasite's virulence ν (i.e., we define virulence as the parasite-induced increase in host mortality; Read 1994). We assume that the parasite is transmitted by contact with either a random individual in the whole population (with probability g_T) or an individual in its local neighborhood (with probability $1 - g_T$). Thus, if the infectivity of infected hosts is given by β and the susceptibility to infection of susceptible hosts by α, the average per capita infection rate of susceptible hosts (or force of infection) is $\alpha\beta[g_T p_I + (1 - g_T)q_{I|S}]$, where $q_{I|S}$ represents the density of infecteds in the neighborhood of an average susceptible and p_I is the global density of infected hosts. Finally, we assume that infected hosts may recover at a fixed rate γ, converting them back into susceptible hosts. This life cycle corresponds to a spatial version of the classical SIS model (Hethcote 2000; see fig. 1 for an illustration and table 1 for a summary of the notation).

With this life cycle, the dynamics of the global densities of susceptible (p_S) and infected (p_I) individuals can be written as

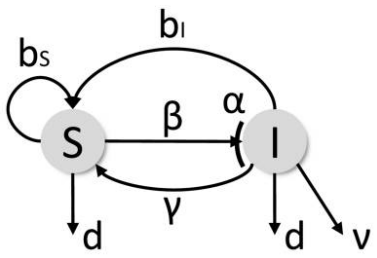

Figure 1: Schematic representation of the life cycle. The hosts can be in two states: susceptible (S) or infected (I). The arrows represent the possible transitions between states, with the associated parameters.

$$\frac{dp_S}{dt} = B_S p_S + B_I p_I - H p_S, \tag{1a}$$

$$\frac{dp_I}{dt} = H p_S - D p_I \tag{1b}$$

(Matsuda et al. 1992; van Baalen and Rand 1998; van Baalen 2002), with the following compound variables:

$$\begin{aligned} B_S &= b_S[(1 - g_R)q_{\circ|S} + g_R p_\circ] - d, \\ B_I &= b_I[(1 - g_R)q_{\circ|I} + g_R p_\circ] + \gamma, \\ H &= \alpha\beta[(1 - g_T)q_{I|S} + g_T p_I], \\ D &= d + \gamma + \nu. \end{aligned} \tag{2}$$

Note that densities are measured relative to the total number of sites, so that $p_\circ + p_S + p_I = 1$. The compound variables B_S and B_I correspond to the net production of new susceptibles by susceptible and infected individuals, respectively; H is the force of infection and measures the rate at which a susceptible host becomes infected (see above). Finally, D corresponds to the rate of disappearance of infected individuals due to either death ($d + \nu$) or recovery (γ). The values of B_S, B_I, and H are not fixed quantities, because they are functions of local densities, which may change over time.

The nonspatial model is obtained by setting g_R and g_T, the proportions of global reproduction and transmission, respectively, equal to unity. On the contrary, when both g_R and g_T are null, all interactions are fully local.

Evolutionary Model

We now study the evolution of host defense traits in a population infected by a single parasite strain. We consider a resident host population with an endemic parasite infection and investigate whether mutant hosts can invade (the conditions for the persistence of the host and parasite populations are derived in app. B, available online). Mutant hosts are initially rare, and their presence does not affect the global dynamics of the resident host population. On the contrary, mutant hosts interact with both resident and mutant individuals, as illustrated in figure 2, which shows a close-up of a cluster of mutants in the early stages of an invasion (see system [C4] in app. C, available online, for the dynamics of the mutant).

We use the next-generation method (Diekmann et al. 1990; Castillo-Chavez et al. 2002; Hurford et al. 2010) to work out the invasion fitness R' of mutant hosts (we write all mutant parameters and variables with primes, while asterisks indicate variables for the resident host at equilibrium). We then assume that selection is weak, that is,

Table 1: Definition and default values of the model's parameters

Symbol	Default value	Description
b_S	5	Fecundity of susceptible individuals
b_I	0	Fecundity of infected individuals
d	1	Natural death rate
α	1	Susceptibility
β	10	Transmissibility
γ	0	Recovery rate
ν	1	Virulence (additional mortality)
a	1, 1.2, 2	Trade-off shape
R_0^{ns}	4	Basic reproductive ratio of the parasite in the nonspatial model
n	6	Number of neighbors
g_R		Proportion of global reproduction
g_T		Proportion of global parasite transmission
p_x		Density of individuals of type x
$q_{x\|y}$		Mean local density of individuals of type x in the neighborhood of an individual of type y
$\bar{q}_{x\|y}$		Mean local density of individuals of type x in the neighborhood of an individual of type y, which is a neutral mutant

Note: The value of R_0^{ns} is given with the default parameters; it changes when the host traits evolve.

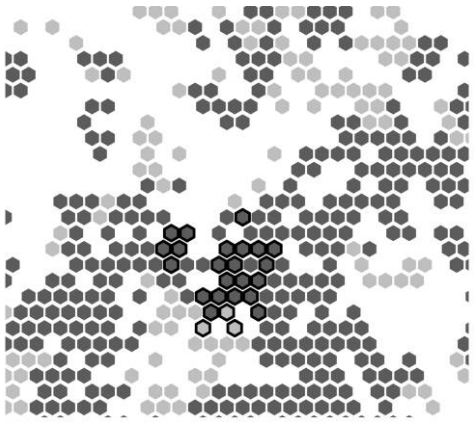

Figure 2: Close-up of a cluster of mutants at the early stages of the invasion on a triangular (six-neighbor) lattice. Dark gray: susceptible host; light gray: infected host; no border: resident host, black border: mutant host with decreased disease transmissibility and fecundity. For resident-host parameters, see table 1; mutant-host parameters that differ from those of resident hosts are $b_S = 4.98$, $\beta = 8.75$.

that all the mutant's parameters are close to the resident's, and derive a selection gradient $\partial R'$ (see app. C for details). Mutants invade only if $\partial R' > 0$. In this spatial model, the mutant can affect its own local environment; therefore, local densities also influence the direction of evolution. Note that no moment-closure approximation (such as the standard pair approximation; Matsuda et al. 1992) is required to derive this selection gradient: we need only equations (1) for resident hosts, and their equivalents for mutant hosts (presented in "Next-Generation Method in Our Model" in app. C). The selection gradient can be written as the sum of four terms,

$$\partial R' = \partial R'_{\text{self}} + \partial R'_{\text{gen}} + \partial R'_{\text{demo}} + \partial R'_{\text{epi}}, \tag{3}$$

where

$$\begin{aligned}\partial R'_{\text{self}} = {} & \frac{\partial b_S[(1-g_R)q^*_{\circ|S} + g_R p^*_\circ] - \partial d}{H^*} \\ & + \frac{\partial b_I[(1-g_R)q^*_{\circ|I} + g_R p^*_\circ] + \partial\gamma}{D^*} \\ & - \frac{B^*_S}{H^*}\frac{\partial\alpha \times \beta[(1-g_T)q^*_{I|S} + g_T p^*_I]}{H^*} \\ & - \frac{B^*_I}{D^*}\frac{\partial d + \partial\gamma + \partial\nu}{D^*},\end{aligned} \tag{4a}$$

$$\partial R'_{\text{gen}} = -(1-g_T)\frac{B^*_S}{H^*}\frac{\alpha\partial\beta\bar{q}_{I'|S'}}{H^*}, \tag{4b}$$

$$\partial R'_{\text{demo}} = +(1-g_R)\left(\partial q_{\circ|S'}\frac{b_S}{H^*} + \partial q_{\circ|I'}\frac{b_I}{D^*}\right), \tag{4c}$$

$$\partial R'_{\text{epi}} = -(1-g_T)\partial(q_{I'|S'} + q_{I|S'})\frac{B^*_S}{H^*}\frac{\alpha\beta}{H^*}, \tag{4d}$$

and

$$\begin{aligned}B^*_S &= b_S[(1-g_R)q^*_{\circ|S} + g_R p^*_\circ] - d, \\ B^*_I &= b_I[(1-g_R)q^*_{\circ|I} + g_R p^*_\circ] + \gamma, \\ H^* &= \alpha\beta[(1-g_T)q^*_{I|S} + g_T p^*_I], \\ D^* &= D = d + \gamma + \nu.\end{aligned}$$

The first term in equation (3), $\partial R'_{\text{self}}$, corresponds to the direct effects of a change in the traits of a focal host on its own fitness. When all interactions are global ($g_R = g_T = 1$), the selection gradient is equal to $\partial R'_{\text{self}}$. The second, third, and fourth terms in equation (3) correspond to effects on fitness due to spatial structure (or interaction environment; Fletcher and Doebeli 2009). Among these, $\partial R'_{\text{gen}}$ takes into account the genetic structure of the environment, via the term $\bar{q}_{I'|S'}$, which is the local density of infected mutants in the neighborhood of susceptible mutants for a neutral mutation and is a measure of interclass relatedness (Lion and van Baalen 2007; see app. C). Apart from genetic structure, mutant individuals can still experience local environments differing from the resident's in terms of demographic and epidemiological structure. The term $\partial R'_{\text{demo}}$ takes into account changes in the demographic structure of the population that result from a change in defense strategy: the terms $\partial q_{\circ|S'}$ and $\partial q_{\circ|I'}$ indeed correspond to the change, compared to resident hosts, in the probability of having an empty site in the neighborhood of susceptible and infected mutant hosts, respectively. The presence of more empty sites ($\circ$) in the neighborhood of mutant individuals means more potential for reproduction, which accounts for the plus sign in equation (4c). The last term, $\partial R'_{\text{epi}}$, expresses changes in the epidemiological structure of the population, via the quantity $\partial(q_{I|S'} + q_{I'|S'})$, which is the change in the probability of having an infected individual (mutant or resident) in the neighborhood of a susceptible mutant host. Having more infected individuals in your neighborhood means that you are more likely to become infected, which, because it is detrimental, accounts for the minus sign in equation (4d).

We want to stress that spatial moment equations (Rand 1999; van Baalen 2002), as we used them to work out the components of the selection gradient, do not require ad-

ditional assumptions about the spatial structure (such as the pair approximation [Matsuda et al. 1992] or other moment-closure methods). Because we also leave open, at this stage, which traits evolve, the expression for the selection gradient that we derive is as general as the underlying epidemiological model.

However, although qualitative observations can be made at this stage, quantitative estimates of the selection gradient require the numerical evaluation of the equilibrium local densities q^* and their sensitivities ∂q to changes in host traits, as these cannot be solved explicitly. To evaluate these quantities, we need to close the system; in what follows, we use the pair approximation (Matsuda et al. 1992; Nakamaru et al. 1997; Boots and Sasaki 1999) to obtain a numerical approximation of these equilibrium densities (see app. E, available online, for details). We then check the generality of these approximations by using individual-based stochastic simulations (see app. D, available online, for a description of our simulations).

We focus, in the remainder of this article, on the evolution of two host defense strategies: increase in additional mortality ν and reduction in transmissibility β. We focus on these traits for two reasons. The first is that such strategies have not been considered as possible components of defense against parasites in theoretical studies, mainly because they are counterselected in nonspatial settings. The second reason is the occurrence of such strategies in various host-parasite systems, which remains largely unexplained. At the end of the article, we discuss the robustness of these results and also summarize results obtained when other host defense traits evolve.

Evolution of Altruistic Host Defense Strategies

We analyze selective pressures on the two host traits separately (additional mortality ν, transmissibility β). For each strategy, we first rewrite the selection gradients for generic parasites and then discuss the qualitative differences between spatial and nonspatial models. First, we consider a simple situation where there is no cost associated with the evolution of each of these defense traits. This allows us to identify and analyze both the direct and the indirect effects associated with the evolution of these traits when they evolve freely. Then, we assume that this evolution is constrained by the existence of life-history trade-offs, for instance, because the defense strategy has pleiotropic effects or because it entails metabolic costs (Boots and Begon 1993; Svensson et al. 1998; Zuk and Stoehr 2002; Tian et al. 2003). Following other studies (Boots et al. 2009), we assume that costs are expressed as reduced fecundities. We checked that costs expressed as decreased survival lead to qualitatively similar results (see fig. A1).

To numerically evaluate the selection gradient, we also have to specify demographic and epidemiological parameters. We first assume that the parasite is very harmful, and we investigate the effects of increasing global interactions and of trade-off shapes. This very harmful parasite castrates its host ($b_{\mathrm{I}} = 0$), and hosts cannot recover from the infection ($\gamma = 0$; see table 1 for the value of the other parameters). Consequently, the compound variable B_{I} is always null: with such a parasite, the infected state is a dead end for the hosts. This type of parasite corresponds, for instance, to lytic bacteriophages (e.g., T-like phages; see Lafferty and Kuris 2009 for other examples). We then check the robustness of our conclusion by changing the values of b_{I} and γ so that the effect of the parasite on host reproduction and recovery is milder. Finally, we run individual-based stochastic simulations to check our conclusions.

Evolution of Additional Mortality (ν)

We begin by focusing on the trait ν, which corresponds to the additional mortality due to the disease. In the absence of cost, the selection gradient with a generic parasite is given by

$$\frac{\partial R'}{\partial \nu} = \underbrace{-\frac{B_{\mathrm{I}}^*}{(D^*)^2}}_{\partial R'_{\mathrm{self}}/\partial \nu} + \underbrace{(1-g_{\mathrm{R}})\left(\frac{\partial q_{\circ|\mathrm{S}'}}{\partial \nu}\frac{b_{\mathrm{S}}}{H^*} + \frac{\partial q_{\circ|\mathrm{I}'}}{\partial \nu}\frac{b_{\mathrm{I}}}{D^*}\right)}_{\partial R'_{\mathrm{demo}}/\partial \nu} - \underbrace{(1-g_{\mathrm{T}})\frac{\partial (q_{\mathrm{I}'|\mathrm{S}'} + q_{\mathrm{I}|\mathrm{S}'})}{\partial \nu}\frac{B_{\mathrm{S}}^*}{H^*}\frac{\alpha\beta}{H^*}}_{\partial R'_{\mathrm{epi}}/\partial \nu}. \quad (5)$$

Note that as mutant hosts have the same transmissibility β as resident hosts, $\partial\beta$ is null, and so is $\partial R'_{\mathrm{gen}}$ (see eq. [4b]). In a nonspatial model, $g_{\mathrm{R}} = g_{\mathrm{T}} = 1$, and the selection gradient reduces to

$$\frac{\partial R'_{\mathrm{ns}}}{\partial \nu} = -\frac{B_{\mathrm{I}}^*}{(D^*)^2}. \quad (6)$$

In this nonspatial model, the selection gradient is thus always negative (or null), which means that smaller values of ν are always selected for (or are neutral). Hence, increased disease-related mortality cannot result from host evolution.

When spatial structure is added, however, indirect fitness effects start to play a role. The direct effect ($\partial R'_{\mathrm{self}}$) remains negative, but $\partial R'_{\mathrm{demo}}/\partial \nu$ and $\partial R'_{\mathrm{epi}}/\partial \nu$ can be positive. The resulting spatial selection gradient can therefore be positive too, so that hosts inducing death when infected can be selected for in the spatial model in the absence of

any trade-off (see fig. A3*A*). This can be understood as follows. Because of population viscosity, mutant hosts are likely to be surrounded by related mutant hosts. Mutant hosts with an increased additional mortality ν are therefore more likely to be surrounded by empty sites (because of the increased death rate of neighbors) than are resident hosts. This accounts for the sign of $\partial R'_{\text{demo}}/\partial\nu$. In addition, as mutant hosts with increased ν have a shorter infectious period, they are less likely to infect their neighbors than are resident hosts; consequently, mutants have fewer infected individuals in their neighborhood, and this accounts for the sign of $\partial R'_{\text{epi}}/\partial\nu$ (see fig. A3*A*).

Increased disease-related mortality is more easily selected for when the first, otherwise negative, term of the selection gradient (eq. [5]) is null, which happens when both b_{I} and γ are null (so that B^*_{I} is null), that is, with our harmful parasite. With milder parasites, the sign of the selection gradient is mainly determined by its first, negative, term, and increased disease-related mortality is less likely to be selected for. Suicide upon infection can thus be an adaptation, but only to extremely harmful parasites.

Costly suicide mechanisms. Defense strategies where mutant hosts have an increased disease-related mortality are found in nature (see, for instance, aborting infection systems in bacteria infected by phages; Labrie et al. 2010). Such strategies may still be costly to maintain. For instance, they may require mechanisms allowing for the detection of the parasite in the host or the maintenance of molecular machineries for committing suicide. Thus, we may assume that an increase in additional mortality due to the infection ν leads to a decrease in host fecundity, and we investigate whether suicide upon infection still evolves with such an additional cost.

In figure 3, we examine the evolution of costly suicide strategies, and we show that such strategies can evolve when interactions are increasingly local (fig. 3*A*) and when the parasite is very harmful, reducing strongly its host's fecundity (b_{I}) and recovery (γ; see fig. 3*B*). These obser-

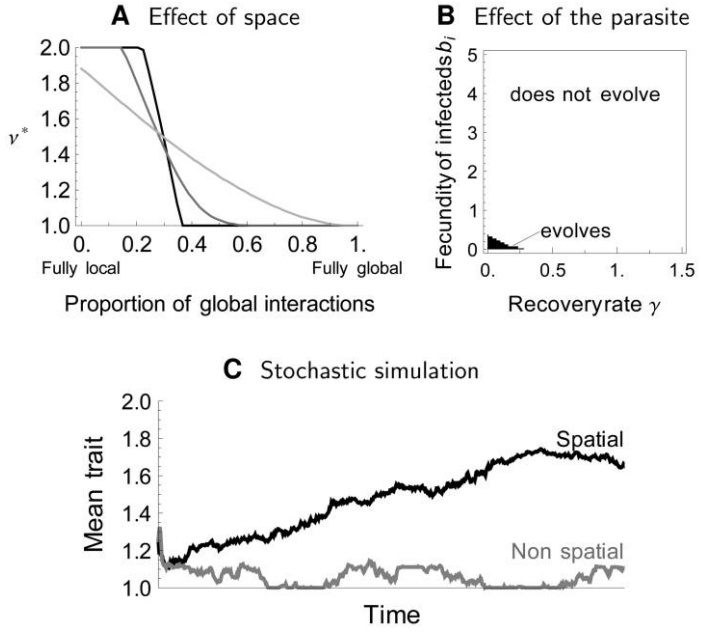

Figure 3: Evolution of costly suicide upon infection. *A*, Predicted attractor values of costly disease-related mortality ν^* with the harmful parasite ($b_{\text{I}} = \gamma = 0$), for different levels of spatial interactions and trade-off shapes. The *X*-axis is $g_{\text{R}} = g_{\text{T}}$, the proportions of reproduction and transmission, respectively, that happen globally. The curves represent different trade-off curvatures: black, linear costs ($a = 1$; see below); dark gray, weakly accelerating costs ($a = 1.2$); light gray, more strongly accelerating costs ($a = 2$). *B*, Whether this strategy evolves with milder parasites, depending on the recovery rate and the fecundity of infected hosts; weakly accelerating trade-off, fully local interactions, $g_{\text{R}} = g_{\text{T}} = 0$. Black, $\nu^* = 2$; white, suicide upon infection does not evolve ($\nu^* = 1$). *C*, Stochastic simulation on a lattice, showing the mean trait value in time, for the fully local ($g_{\text{R}} = g_{\text{T}} = 0$, black curve) and fully global ($g_{\text{R}} = g_{\text{T}} = 1$, gray curve) models, with the harmful parasite ($b_{\text{I}} = \gamma = 0$). Default parameters are given in table 1. Evolving parameters: trait, $\nu(\rho) = 1 + \rho$ (ρ between 0 and 1 so that the values of ν are constrained between 1 [nonresistant host] and 2 [most resistant host]); cost, $b_{\text{S}}(\rho) = 5 - 0.1\rho^a$. In *B* only, $b_{\text{I}}(\rho) = \max(b_{\text{I}} - 0.1\rho^a, 0)$. Trade-off shapes: $a = (1, 1.2, 2)$ in *A*; $a = 1.2$ in *B* and *C*.

vations are confirmed by stochastic individual-based simulations on regular lattices (see fig. 3*C*).

Evolution of Transmissibility (β)

Here, we study a second kind of defense, which corresponds to a decreased transmissibility (β). Mutants with a decreased transmissibility are less likely to transmit the disease than resident hosts but have the same susceptibility (α) to the disease. Note that transmissibility is a trait that characterizes infected hosts; this defense mechanism hence fundamentally differs from avoidance, which corresponds to decreasing the chance of becoming infected and is a trait associated with susceptible hosts (corresponding to a decrease in the parameter α in our model). We start by studying the effect of decreased transmissibility alone, in the absence of any cost.

In the absence of costs, the selection gradient becomes

$$\frac{\partial R'}{\partial \beta} = \underbrace{-(1-g_{\mathrm{T}})\frac{B_{\mathrm{S}}^{*}}{H^{*}}\frac{\alpha \bar{q}_{I'|S'}}{H^{*}}}_{\partial R'_{\mathrm{gen}}/\partial \beta} + \underbrace{(1-g_{\mathrm{R}})\left(\frac{\partial q_{\circ|S'}}{\partial \beta}\frac{b_{\mathrm{S}}}{H^{*}} + \frac{\partial q_{\circ|I'}}{\partial \beta}\frac{b_{\mathrm{I}}}{D^{*}}\right)}_{\partial R'_{\mathrm{demo}}/\partial \beta} - \underbrace{(1-g_{\mathrm{T}})\frac{\partial (q_{I'|S'}+q_{\mathrm{I}|S'})}{\partial \beta}\frac{B_{\mathrm{S}}^{*}}{H^{*}}\frac{\alpha \beta}{H^{*}}}_{\partial R'_{\mathrm{epi}}/\partial \beta}. \quad (7)$$

In a nonspatial model, where $g_{\mathrm{R}} = g_{\mathrm{T}} = 1$, the selection gradient reduces to

$$\frac{\partial R'_{\mathrm{ns}}}{\partial \beta} = 0. \quad (8)$$

This means that in a nonspatial model, whichever the parasite (harmful or not), mutant hosts with a different disease transmissibility are neither favored nor disfavored and are thus selectively neutral. Such a mutation brings no benefit to the hosts, because it prevents them neither from getting infected nor from suffering from the disease.

However, the terms corresponding to effects on fitness due to the spatial structure are typically no longer null once some spatial structure is introduced. Numerical resolutions with the harmful parasite show that the fitness effect due to the genetic structure of the population ($\partial R'_{\mathrm{gen}}$) is positive (so that we have $\partial R'_{\mathrm{gen}}/\partial \beta < 0$, as mutants have a reduced transmissibility; see fig. A3*B*); this is due to the fact that the probability for a neutral susceptible mutant to have an infected mutant in its local neighborhood ($\bar{q}_{I'|S'}$) is not null. This local density $\bar{q}_{I'|S'}$ is a measure of interclass relatedness (Lion and van Baalen 2007); this term matters because reduced transmissibility brings an indirect fitness benefit to an infected mutant host only if this reduces the force of infection toward related susceptible hosts. Contrary to the evolution of ν, here the other two effects of the spatial structure are weak and favor increased transmissibility (see fig. A3*B*).

Evolution of decreased transmissibility with a fecundity cost. Because the effect of decreased transmissibility becomes neutral when interactions are more and more global, the addition of a fecundity cost always leads to the counterselection of this defense strategy with global interactions (see fig. 4*A*). With more local interactions, however, kin selection enables the evolution of decreased transmissibility (see fig. 4*A*): even though this strategy does not bring any direct benefit to the bearer of the mutation, related hosts benefit from it. In addition, this strategy can evolve even in the presence of milder parasites (see fig. 4*B*). Such a defense strategy can thus also be seen as a form of "altruistic resistance." Stochastic simulations on a regular lattice confirm these predictions (fig. 4*C*).

Discussion

In this article, we have investigated the effect of spatial structure on the evolution of host defense components. Assuming weak selection, we derived analytical expressions of selection gradients, in both spatial and nonspatial models, that helped disentangle the different effects of space: we distinguished between effects of the genetic structure of the population and effects of changes in the demographic and epidemiological structures of the population. We numerically solved the model—now using the pair approximation—with specific parameters in order to quantitatively evaluate how changes in each host life-history trait influenced the local densities. We focused on the evolution of two altruistic host defense strategies. These strategies consist of limiting the spread of parasites through a decrease in the life span (ν) or the disease transmissibility (β) of infected hosts.

We first investigated the evolution of disease-related mortality ν in the absence of pleiotropic costs. When the parasite sterilizes its hosts and cannot be cleared by them, it converts its hosts into "zombies" that transmit the disease but cannot contribute to the growth of the population. In a nonspatial setting, there is no selection on hosts to change their disease-related mortality ν, because there is no benefit in remaining in a nonreproducing and nonrecovering state for longer. In a spatial setting, however, ν affects the local demographic and epidemiological structures in such a way that it may become advantageous for the hosts to increase their disease-related mortality. We then assumed that there were fecundity costs to an increased disease-related mortality and confirmed that this defense strategy was counterselected when interactions are

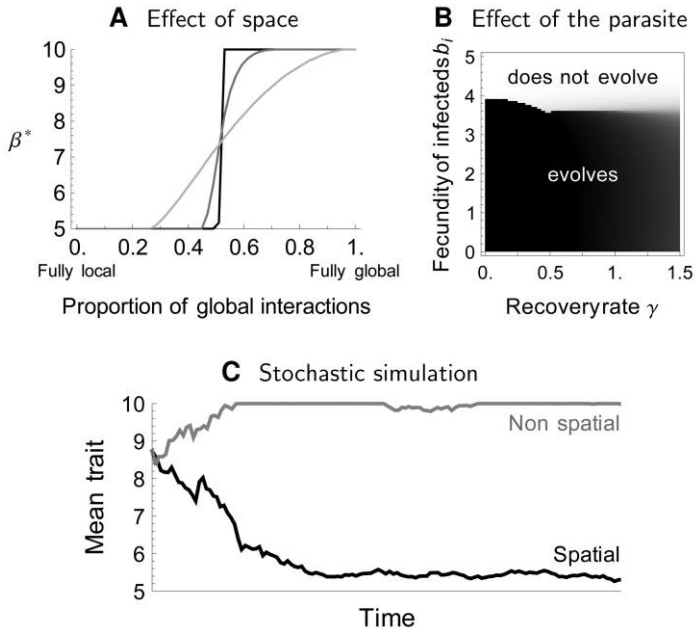

Figure 4: Evolution of costly reduced transmissibility. *A*, Predicted attractor values of disease transmissibility β^* with the harmful parasite ($b_I = \gamma = 0$), for different levels of spatial interactions and trade-off shapes. The *X*-axis is $g_R = g_T$, the proportions of reproduction and transmission, respectively, that happen globally. The curves represent different trade-off curvatures: black, linear costs; dark gray, weakly accelerating costs; light gray, more strongly accelerating costs. *B*, Whether this strategy evolves with milder parasites, depending on the recovery rate and the fecundity of infected hosts; weakly accelerating costs, fully local interactions, $g_R = g_T = 0$; black, $\beta^* = 5$ (fully resistant); gray, intermediate β^*; white, the strategy does not evolve ($\beta^* = 10$). *C*, Stochastic simulation on a lattice, showing the mean trait value in time, for the fully local ($g_R = g_T = 0$, black curve) and fully global ($g_R = g_T = 1$, gray curve) models with the harmful parasite ($b_I = \gamma = 0$). Default parameters are given in table 1. Evolving parameters: trait, $\beta(\rho) = 10 - 5\rho$ (ρ between 0 and 1 so that the values of β are constrained between 10 [nonresistant host] and 5 [most resistant host]); cost, $b_S(\rho) = 5 - 0.1\rho^a$. In *B* only, $b_I(\rho) = \max(b_I - 0.1\rho^a, 0)$. Trade-off shapes: $a = (1, 1.2, 2)$ in *A*; $a = 1.2$ in *B* and *C*.

global, while it can be selected for when there are both more local interactions and harmful parasites. Spatial structure can hence favor the evolution of suicide upon infection (see fig. 3*A*, 3*C*). Interestingly, such parasite-induced suicides have been reported in bacteria infected by bacteriophages. Aborting infection systems, such as the Rex system, indeed abort phage infection, by targeting important steps for phage multiplication, but a side effect is the death of the host bacterium (Labrie et al. 2010). This effect is, however, observed only when the parasite is very harmful (γ and b_I close to 0). Conversely, when infected hosts contribute enough to the growth of the population, suicide upon infection does not evolve (see fig. 3*B*).

We showed that spatial structure can also promote the evolution of a decrease in transmissibility β. In a spatially structured environment, this defense mechanism can evolve because of beneficial indirect effects to related neighbors (see fig. 4), which corresponds to the genetic component of our partitioning of the effects of space. This form of defense occurs in various species. For instance, many aphids release cornicle secretions upon attack by parasitoids. This induces a fitness cost (Mondor and Roitberg 2003) and brings no direct benefit to the aphid that released the cornicle secretion, but it is beneficial for other aphids in the colony, which are less likely to be infected (Wu et al. 2010). Another example of this altruistic resistance strategy is the development of transmission-blocking immunity in vertebrates infected by *Plasmodium*, the agent of malaria. This immunity is antibody mediated and is directed toward the sexual stages of the parasite, which develop in the mosquito (Mendis et al. 1987). Hence, the production of these antibodies does not directly benefit the individual, but it may benefit its kin via a reduction of parasite transmission. Finally, recent studies have shown that infected social insects—ants (Heinze and Walter 2010) and bees (Rueppell et al. 2010)—actively leave their colonies to die in isolation. This behavior prevents the spread of the disease among nestmates (decreased β), and the isolated individuals have a reduced survival outside of the colony (increased ν). Although our model does not match the specific features of these host-parasite systems, it high-

lights the fact that the evolution of host defense has to be envisioned at a higher level—host clusters (which emerge in spatially structured populations; van Baalen and Rand 1998) or host groups (such as colonies)—rather than at a purely individual level.

Other Host Traits

To illustrate the effect of spatial structure on the evolution of host defense, we focused on two traits, additional disease-related mortality and decreased transmissibility, because these strategies have been largely overlooked in theoretical studies on the evolution of host defense, even though they occur in nature. Another reason for this choice is the strong qualitative differences in the selection gradients in nonspatial and spatial models (compare eqq. [6] and [8] to eqq. [5] and [7], respectively), which allowed us to predict the evolution of those strategies without having to numerically evaluate the selection gradient, and therefore without making any additional assumption regarding the spatial structure (i.e., no pair approximation).

Our general model can also be used to study the evolution of other strategies, such as avoidance (i.e., decrease in susceptibility α, a strategy of resistance; Roy and Kirchner 2000; Best et al. 2011) or disease tolerance (i.e., decrease in disease-related mortality ν). Our results indicate that spatial structure may favor the evolution of costly decreased susceptibility (as observed by Best et al. 2011). In contrast, we find that tolerance spreads less easily in spatial settings (see fig. A2; note that a necessary condition for the evolution of tolerance is the possibility that hosts can clear the disease or reproduce when infected, i.e., that b_{I} and γ are both nonzero). Mutants with a reduced ν live longer and therefore free up fewer sites than resident individuals; in addition, such tolerant mutants have a longer infectious period and are therefore more likely to infect their neighbors than are resident individuals. Hence, a beneficial effect of the mutation on the mutant itself is counterbalanced by detrimental effects on its neighborhood.

We focused in this study on traits directly related to the host-parasite interaction, but one could also consider other host traits. For instance, one could look at the evolution of host fecundity as a response to parasitism. The effect of such a change in reproductive effort could be considered another tolerance trait: a trait that compensates for the expected reduction of life span by an increase in reproductive output. Such strategies have been reported in several organisms (Krist 2001; Granovitch et al. 2009) and studied in nonspatial models (Gandon et al. 2002; Best et al. 2009). Yet the potential effect of spatial structure on this evolution remains to be explored. Another host trait one could look at is the natural death rate d. Mitteldorf and Pepper (2009) recently showed that senescence can evolve as an adaptation protecting against infectious diseases. Preliminary investigations with our model show that an increased natural death rate can evolve in a spatial model as a result of indirect selective effects but that such an evolution is possible only with a very harmful parasite whose overall transmission (the product of α and β) is very high (which is consistent with the fact that $\alpha\beta$ tends to infinity in the model of Mitteldorf and Pepper 2009).

Perspectives and Future Work

We considered a limited number of scenarios in this study, but the general selection gradient we derived applies to other situations as well, and it can be seen as a toolbox for further studies. For the sake of simplicity, however, we have not considered some features of host-parasite interactions, and this may call for further refinements of our model.

First, we considered in our model a specific—but classical on lattices—form of density dependence. In our spatial model, hosts live on a lattice, each site can contain at most one individual, and offspring can survive only in empty sites. The maximal number of individuals is the number of sites on the lattice. But some studies of host evolution in nonspatially structured environments take into account the potential effect of the sensitivity to crowding (e.g., van Baalen 1998; Boots and Bowers 1999; Gandon et al. 2002). The way we modeled density dependence in our model corresponds to a parameter of sensitivity to crowding $\kappa = 1$ in van Baalen (1998) and Gandon et al. (2002) models. A different form of density dependence could be modeled by allowing reproduction in already occupied sites, followed by competitive replacement (Lion and Gandon 2009).

Second, we looked at defense traits individually, but host defense strategies are likely to involve different traits at the same time (Råberg et al. 2007; Boots 2008). Restif and Koella (2004) considered the joint evolution of defense traits in a nonspatial model; spatial structure may alter their predictions, as resistance strategies are more favored with local interactions (Best et al. 2011), while tolerance can be less favored (see fig. A2).

Third, the ∂q terms in the components $\partial R'_{\mathrm{demo}}$ and $\partial R'_{\mathrm{epi}}$ (see eqs. [4]) of the selection gradient are likely to depend themselves on measures of genetic structuring, as found in models on the evolution of helping and parasite life-history traits (Rousset and Ronce 2004; Lion and Gandon 2009; Lion and Boots 2010). Finding out their expressions will not be straightforward but is certainly worth investigating in further studies.

Finally, we assumed in this study that the parasites were genetically identical; the underlying assumption in studies

on the evolution of host defense is that hosts evolve faster than parasites. This is clearly unrealistic for many host-parasite interactions, which has led several authors to consider the coevolution of hosts and parasites (e.g., van Baalen 1998; Gandon et al. 2002; Restif and Koella 2003; Svensson and Råberg 2010; Best et al. 2011). Best et al. (2011), for instance, explored such a coevolution between parasite virulence and host susceptibility (parameter α in our model). Hence, our theoretical framework could be extended to study the coevolution between parasites and many other host defense strategies.

To conclude, spatial effects may blur the distinction between resistance and tolerance strategies, which has been the subject of much debate (Råberg et al. 2007; Little et al. 2010). In particular, this may lead us to reconsider the level at which a defense strategy is defined (individual vs. cluster level). But beyond these conceptual issues, basic experimental evidence of these spatial effects on host defense evolution is still lacking. We hope that the theoretical recognition of the effect of spatial structure that we provide here will motivate further experimental studies in different biological systems.

Acknowledgments

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APPENDIX A

Supplementary Figures

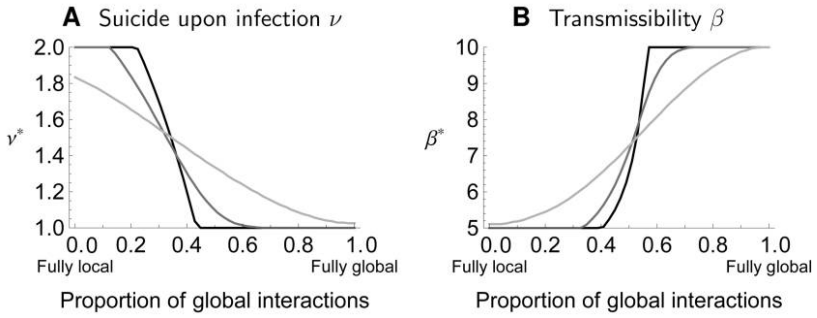

Figure A1: Convergence stable singular strategies, as a function of the proportion of global interactions ($g_R = g_T$), when the cost is on survival (d) instead of fecundity. *A*, Equivalent of figure 3*A*; *B*, equivalent of figure 4*A*. Black curves, linear costs; dark gray curves, weakly accelerating costs; light gray curves, more strongly accelerating costs.

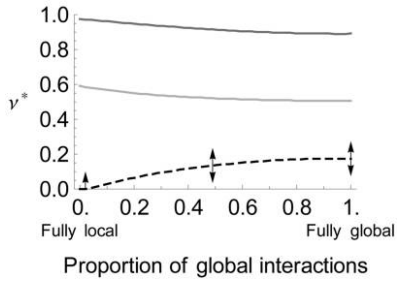

Figure A2: Evolution of costly decreased disease-related mortality, or tolerance. The solid (dashed) curves show the predicted attractor (repellor) values of disease-related mortality ν^* with a mild parasite ($b_I = 2$, $\gamma = 0.5$), for different levels of spatial interactions. The *X*-axis is $g_R = g_T$, the proportions of reproductions and transmissions that happen globally. The curves represent different trade-off curvatures: black, linear costs; dark gray, weakly accelerating costs; light gray, more strongly accelerating costs. The values of ν are constrained between 1 (nontolerant host) and 0 (most tolerant host).

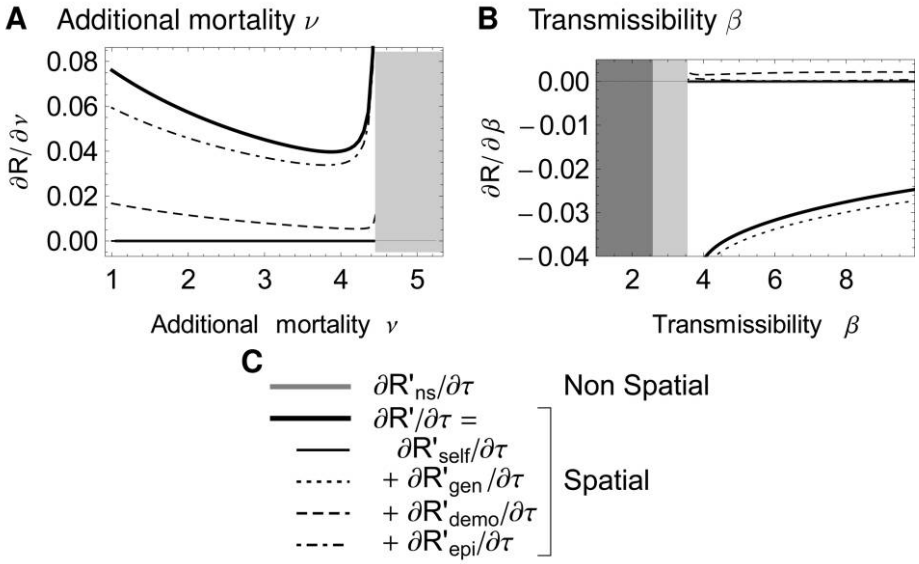

Figure A3: *A*, Selection gradient $\partial R'/\partial \nu$ and its decomposition, in the absence of costs, as a function of the host additional mortality due to the disease ν in the spatial model (thick black curve) and in the nonspatial model (thick gray curve). The selection gradient vanishes when ν is too high for parasites to persist. *B*, Selection gradient $\partial R'/\partial \beta$ and its decomposition, in the absence of costs. *C*, Legend. For the values of fixed parameters, see table 1.

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