Strategies of host resistance to pathogens in spatially structured populations: An agent-based evaluation.

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Abstract

There is growing theoretical evidence that spatial structure can affect the ecological and evolutionary outcomes of host-parasite interactions. Locally restricted interactions have been shown in particular to affect host resistance and tolerance. In this study we investigate the evolution of several types of host disease resistance strategies, alone or in combination, in spatially structured populations. We construct a spatially explicit, individual-based stochastic model where hosts and parasites interact with each other in a spatial lattice, and interactions are restricted to a given neighbourhood of varying size. We investigate several host resistance strategies, including constitutive (expressed in all resistant hosts), induced (expressed only upon infection), and combinations thereof. We show that the specific resistance mechanism against a pathogen as well as the size of the neighbourhood both affect resistance spread and parasite dynamics, an effect modulated by the level of the cost of resistance. Our results shed new light on the dynamics of disease resistance in a spatially-structured host-pathogen system, and illustrate the conditions in which a variety of resistance mechanisms can be maintained, including when they are costly. Overall these results advance our theoretical understanding of the evolutionary dynamics of disease resistance, a necessary step to elaborate more efficient and sustainable strategies for disease management.

Keywords: host-parasite interactions; defence; resistance; transmission; recovery; altruism; space.

42

43 **1. Background**

44 Host resistance to pathogens presents an obvious evolutionary advantage and, because
 45 of the ubiquity of parasitism in the living world, such traits are typically and pervasively
 46 under strong, positive selection. Resistance, however, is usually associated with a fitness cost
 47 for the host, and therefore also subject to negative selective pressure. Such costs of resistance
 48 have been demonstrated in many organisms ranging from bacteria [1] to insects [2, 3] and
 49 plants [4]. The balance between these selective forces drives the evolution of resistance in
 50 host-parasite systems.

51 There is now growing evidence that the spatial structure of populations can affect this
 52 selective balance, and therefore affect the ecological outcomes of host-parasite interactions,
 53 and ultimately the epidemiological dynamics of diseases. In theoretical models [5], locally
 54 restricted interactions between hosts and pathogens have been shown to favour host resistance
 55 when compared to well-mixed population models [6]. In addition, the evolution of host
 56 tolerance has been shown to be restricted in spatially explicit population models [7].

57 All the aforementioned factors (pathogen pressure, costs of resistance, spatial
 58 population structure) paint the picture of a complex selective landscape for host resistance to
 59 disease. Consequently, depending on the specific host and pathogen species of interest, as
 60 well as ecological and epidemiological characteristics of the considered system, it is likely
 61 that the actual selection pressures would differ substantially and, as a corollary, that different
 62 resistance strategies would be favoured by selection. Generally speaking, resistance strategies
 63 can differ in the mechanism itself (e.g. specific immune pathways), in the quantitative
 64 investment in the response, or in the timing of the response (e.g. constitutive expression of
 65 immune components versus induced expression in response to an infection).

The purpose of this study is therefore to further characterize the dynamics of the evolution of resistance strategies in a spatially-structured host-parasite system, with a specific focus on the different types of resistance (and combinations thereof) that a host can possibly mount and the corresponding impacts of the associated resistance costs.

To that end, we present in this article a spatially explicit, individual-based stochastic model, simulating host and pathogen populations and their interactions. The spatial architecture of this model allows us to restrict to a given neighbourhood (of varied size) the biological and ecological processes in the model, such as pathogen transmission dynamics, host reproduction, and migration, and therefore to control the level of spatial structure in the population. Within this (more or less) spatially restricted framework we examine the fate of a variety of host resistance strategies against a generic pathogen. In particular we consider whether resistance (and its associated costs) is constitutively expressed in resistant hosts or induced by the response to an infection (and therefore not expressed in uninfected hosts). We also distinguish between responses aimed at stopping forward transmission versus clearing an existing pathogen in an infected host.

In the following sections, we first present the details of the model features and parameterization. We then present the result of model simulations that examine resistance strategies based on constitutive response, induced responses affecting transmission or recovery, or a mix thereof, all under various levels of spatial population structure (i.e. locally restricted interactions). We demonstrate that the evolution of resistance in a spatial setting depends on the type of resistance and the conditions in which it is mounted by the host, along with the costs associated with each type of resistance. We conclude by discussing the evolutionary consequences of these observations for host-pathogen and disease systems.

2. Model

91 **2.1 General model characteristics**

92 We introduce in this study a probabilistic cellular automaton, a stochastic, spatially-
 93 explicit individual-based model. The population is described as a square, homogeneous
 94 100x100 lattice of individual sites, each of which may be empty or occupied by a single
 95 (infected or uninfected) host. To eliminate edge effects, we assume that the lattice has a toric
 96 topology, i.e. sites on a given edge are connected to sites on the opposite edge. The source
 97 code for the simulation is available on request.

99 **2.2. Host genotypes and resistance**

100 Hosts can be classified into two main genotypes according to their ability to respond
 101 to a pathogen. Susceptible hosts are completely vulnerable to pathogens and not able to mount
 102 any response to infection. Resistant hosts are able, through immune responses, to resist
 103 infection to some extent (see details below, depending on the mode of resistance and the
 104 investment in the response).

105 We consider a variety of response strategies that resistant hosts can mount against
 106 pathogens. First, we distinguish between constitutive and inducible immune responses. A
 107 constitutive response is expressed by all resistant hosts regardless of their infection status,
 108 whereas an inducible response is only expressed upon infection. A given host can express a
 109 mixture of these two strategies, where the ratio of investment in constitutive response is
 110 defined as r_1 (in other words, if $r_1=1$, then the response is strictly constitutive, and
 111 conversely, strictly inducible when $r_1=0$).

112 The constitutive immune response, being expressed at all times, is considered here
 113 equivalent to a barrier to infection. Thus, in our model, the constitutive immune response
 114 affects the probability, for a given uninfected host, of becoming infected. An inducible
 115 response, on the other hand, being only expressed upon infection, can only affect the

pathogen dynamics within an infected host, or its ability to infect other hosts. Consequently, we distinguish in our model two modes of action for an inducible response: one affecting the clearance rate of the infection, the other affecting the forward transmissibility of the parasite to other hosts. The investment in one or the other is determined by a factor called r_2 . If $r_2 = 1$, the response affects only the clearance, whereas only transmissibility is reduced when $r_2 = 0$. This means that inducible strategies can exist along a continuum going from purely inward strategies targeted at the infected individual itself (i.e. focused on clearing the infection, $r_2 = 1$) to outward strategies targeted at its interactions with neighbours (i.e. focused on blocking forward transmission, $r_2 = 0$, where the resistant individual gets no direct benefit).

Resistance is also characterized by a given efficacy (eff_1 or eff_2 for constitutive and inducible responses respectively) negatively affecting the parasite fitness in a manner depending of the type of resistance. When considering one single response, the efficacy of resistance is always total (equal to 1) whereas in the case of multiple responses the efficacy is directly related to the ratio of the investment in the given responses.

2.3. Model dynamics

At each time step, the model is iterated through the following processes in the following order (each detailed below): reproduction, movement, death and change in infectious status (infection, recovery). In this agent-based framework, local interactions are restricted to individuals within a given neighbourhood. In this study we use van Neumann neighbourhoods, with sizes (sz) varying between 1 and 5, where the size of the neighbourhood corresponds to the maximum Manhattan distance (distance between two points in a grid based on a strictly horizontal and/or vertical path) between neighbours. The higher the value is, the less viscous is the population, i.e. closer to a non-structured, well-

mixed system. This type of spatial structuration and the associated levels of population viscosity have indeed been shown to influence the evolution of a variety of life-history traits in host parasite systems. Pathogens in spatially structured population tend to evolve lower transmission rate and virulence as shown in theoretical approaches (Boots and Sasaki, 1999; Kamo et al. 2007; Lion and Boots, 2010) or via empirical studies (Kerr et al. 2006; Boots and Meador 2007), whereas localized transmission and host reproduction can select for a higher host resistance (Best et al. 2011).

2.3.1. *Reproduction*

Each individual can give birth by asexual reproduction to one uninfected (no vertical transmission) offspring per time step. This offspring is of the same genotype and expresses the same type of immune response (if any). The nominal birth rate, denoted rH , is the same for infected and uninfected individuals as we assume that fecundity is not affected by the infection (and that pathogen virulence only affects survival, see below).

In a similar manner as done in previous studies [6, 8] resistance is assumed to be associated with a cost leading to a reduced fecundity of the resistant individuals by a factor $(1-cR)$, where cR is the cost of resistance.

All resistant individuals pay the cost of a constitutive resistance, and the reduction of fecundity is defined as:

$$(1-cR) = (1-c1) = (1-cMax1*eff1^{m1}) \quad (\text{Eq. 1})$$

Concerning the induced resistance, only the infected resistant individuals (as resistance is only expressed during infection) pay the associated cost. The reduction of fecundity is then defined as:

$$(1-cR) = (1-c2) = (1-cMax2*eff2^{m2}) \quad (\text{Eq. 2})$$

When both responses are combined then the cost paid by the infected individuals is assumed to be multiplicative:

$$(1-cR) = (1-c1)*(1-c2). \quad (\text{Eq. 3})$$

In Eq. 3 and 4, both $m1$ and $m2$ represent the departure from linearity. The higher their value is, the lower the cost is at low levels of investment, i.e. efficacy. A list of model parameters, along with their definition and the range of explored values, is given in Table 1. Table 2 recapitulates the host life history traits for various types of hosts based on these parameters.

Table 1: Definitions and range of values of the model parameters.

Parameter	Definition	Range of values
cMax1	Maximal cost of resistance of the constitutive immune response	0 - 1
cMax2	Maximal cost of resistance of the inducible immune response	0 - 1
r1	Ratio of the investment between the constitutive immune response and the inducible one(s)	0 - 1
r2	Ratio of the investment between the inducible recovery-boosting and inducible transmission-blocking responses	0 - 1
rH	Birth rate of a susceptible (S) individual	0.02 - 0.08
β_0	Transmission rate from an infected susceptible (I) individual	0.125 - 0.5
α	Virulence of the parasite (additional mortality)	0.125 - 0.5
μ	Death rate of a susceptible (S) individual	0.1
γ	Recovery rate of the infected susceptible (I) individual	0.1
eff1	Efficacy of the constitutive resistance	0 - 1
eff2	Efficacy of the inducible resistance	0 - 1
sz	Neighbourhood size	1 - 5
m1 - m2	Departure from linearity	1.4

Table 2: Life-history traits of the different types of hosts and epidemiological parameters of the model

	Susceptible Uninfected	Susceptible Infected	Resistant Uninfected	Resistant Infected
Reproduction	rH	rH	$rH(1-c1)$	$rH*(1-c1)*(1-c2)$
Mortality	μ	$\mu(1+\alpha M)$	μ	$\mu*(1+\alpha)$
Transmission Rate	0	β_0	0	$\beta_0*(1-eff2*(1-r2))$
Clearance	-	γ	-	$1-(1-\gamma)*(1-eff2*r2)$
Cost of the Constitutive Resistance (c1)	-	-	$cMax1*eff1^{m1}$	$cMax1*eff1^{m1}$
Cost of the Inducible Resistance (c2)	-	-	-	$cMax2*eff2^{m2}$

Host reproduction is implemented as a two-step process. First, there is a random choice of a number between 0 and 1 (uniform distribution). If its value is lower than the reproduction rate, then there is a second draw choosing a random site (with equiprobability for each site) in the neighbourhood. If it is an empty one, then the offspring occupies this site, otherwise there is no reproduction for the host at this given round. The reproduction process is therefore density-dependent, and the nominal birth rate r_H represents the optimal reproduction rate for an isolated individual. During this process, it is obvious that the density-dependence advantages the first hosts being selected by the algorithm. To avoid systematically favouring specific locations in the lattice, hosts are treated in a random order at each time step.

2.3.2. Movement

A Bernoulli trial determines the occurrence of movement for a given host with a probability given by the movement rate. If movement occurs, a destination site is chosen at random in the neighbourhood. If it is an empty site, then the host moves, otherwise the host stays in the site. When movement occurs, the genotype of the host and its infection status remain unchanged.

2.3.3. Death

Individuals are removed from the population at a mortality rate that depends on the infectious status. Each host may die at each time step based on the outcome of a Bernoulli trial with a probability given by the mortality rate. At the end of this step, a snapshot of the grid is done in order to record all information needed to evaluate the next processes.

2.3.4. State change: Infection

In the spatial model, the parasite can be transmitted from an infected host to uninfected hosts among its neighbours in a frequency-dependent manner. For a given uninfected host, the rate of infection depends on the presence of infected hosts in the neighbourhood. Each infected neighbour's ability to transmit the parasite is characterized by a probability of infection, denoted β , that is a measure of the parasite's success in transmission. If this infected host has a resistant genotype with an inducible response acting on transmission ($r_2 < 1$), the probability of infection from this particular host is reduced by a factor $(1 - \text{eff}_2 * (1 - r_2))$.

For a given uninfected host, the probability of infection is then calculated as the probability of successful transmission by at least one of its infected neighbours. A random number between 0 and 1 (uniform distribution) is then drawn and if it is lower than this probability of infection, transmission occurs. Resistant individuals expressing a constitutive response with efficacy eff_1 have a probability to become infected that is reduced by a factor $(1 - \text{eff}_1)$. Resistant individuals expressing an inducible response, on the other hand, have the same probability to be infected than the susceptible ones. Table 3 describes the pairwise probability of infection of a host X by a host Y.

Table 3: Probability of infection of an uninfected host X by an infected host Y.

X \ Y	Susceptible	Resistant
Susceptible	β	$\beta * (1 - \text{eff}_2 * (1 - r_2))$
Resistant	$\beta * (1 - \text{eff}_1)$	$\beta * (1 - \text{eff}_2 * (1 - r_2)) * (1 - \text{eff}_1)$

2.3.5. *State change: Recovery*

Individuals can recover from infection with a rate γ . The recovery rate can be affected by the investment in the inducible defence and in this latter case, the recovery rate becomes:

$$1 - (1 - \gamma) * (1 - \text{eff}_2 * r_2). \quad (\text{Eq. 4})$$

In a similar manner as for the previous events, if the recovery rate is lower than a randomly drawn number chosen between 0 and 1, then the individual remains infected.

2.3.6. *Simulations*

In each simulation, the lattice is initially populated with 1000 individuals of the susceptible genotype including 20% of infected, all randomly distributed between sites. The simulation is first run for 1000 time steps to allow the resident population to equilibrate. 100 non-infected invading resistant hosts are then introduced into sites randomly selected among the available empty sites in the lattice. The simulation is run for 250 000 iterations or stopped earlier if one genotype reaches fixation. Except when stated otherwise, five replicates are done for each set of parameters.

3. Results

In the first two scenarios, we only explored the effect of space on the spread of one type of resistance alone, first the constitutive one, then the inducible one. To do so the r_1 parameter was respectively set to 1 then 0. We varied the cost associated with each type of resistance, as well as the size of the neighbourhood, in order to measure their combined impact on the spread of resistance in the host population as well as on the epidemiology of the disease.

3.1. Constitutive resistance alone ($r_1=1$)

As mentioned earlier constitutive resistance is associated with a fixed cost (paid by both infected and non-infected individuals). As there is only a single type of resistance involved, the value of this cost is c_{Max1} . We observe that for all neighbourhood sizes a moderately high cost ($cost > 0.1$) precludes the spread of resistance altogether (Figure 1). Fixation of the resistant genotype can only occur when resistance is not costly. In those instances, the parasite is then always eliminated from the population at the end of the corresponding simulations. The parasite can also be eliminated from the population for a range of low, non-zero values of cost, in which case the resistant genotype is then unsurprisingly lost as a consequence of this cost.

The size of the neighbourhood affects both resistance spread and parasite dynamics. We observe that, for a given cost, resistance can spread to higher frequencies when neighbourhood size is larger (Figure 1A). These results are confirmed with a simple statistical analysis (Table 4)

Table 4. Logistic analysis of the spread (presence/ absence) of a costly constitutive defence response in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	9.42	0.052
Cost of resistance	1	47.39	<0.0001
Cost of resistance x Size of the neighbourhood	4	1.917	0.751
Replicate	4	0.864	0.929

Figure 1A. Effect of the fitness cost of resistance (c_{Max1}) and of the size of neighbourhood on the spread of a constitutive resistance against a pathogen and on the parasite presence at equilibrium. The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $r_H=0.02$, efficacy of resistance $eff_1=1$, departure from linearity $m_1=1.4$, level of investment in the constitutive resistance $r_1=1$.

Additionally, we observe that in larger neighbourhoods, parasites can be eliminated from the population at higher values of cost of resistance. It is noteworthy that parasites are eliminated at a higher speed for low values of the cost of resistance (Figure 1B).

Figure 1B. Effect of the fitness cost of a constitutive resistance against a pathogen and of the size of neighbourhood on the speed of elimination of a parasite. The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $r_H=0.02$, efficacy of resistance $\text{eff}_1=1$, departure from linearity $m_1=1.4$, level of investment in the constitutive resistance $r_1=1$. The regression lines in the graphs are built for each size of neighbourhood with the points for which the parasite is still present.

3.2. Inducible defences alone ($r_1=0$)

As mentioned in the Methods, in the case of inducible defence, we explore two distinct mechanisms, either blocking forward transmission (reducing β) or boosting recovery (increasing γ). The ratio of the investment in each mechanism is given by r_2 , where $r_2=0$ corresponds to an exclusive investment in transmission-blocking response, and $r_2=1$ to an exclusive investment in recovery-boosting response. We first examine each of these responses separately.

3.2.1. Transmission-blocking response ($r_1=0$ and $r_2=0$)

The size of the neighbourhood has a strong impact on the spread of this type of resistance (Table 5). We observe that when the cost of resistance increases, resistance spreads more easily in smaller neighbourhoods (S1 Figure).

Table 5. Logistic analysis of the spread (presence/ absence) of a costly inducible transmission-blocking defence response in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	38.92	<0.0001
Cost of resistance	1	2.60	0.1071
Cost of resistance x Size of the neighbourhood	4	7.46	0.11
Replicate	4	2.73	0,60

The resistant genotype can be maintained in our simulations with relatively high values of the cost of resistance only in the smallest neighbourhood (size 1 and 2) and only in simulations where the parasites are eventually lost from the population. In the largest neighbourhoods resistance cannot become fixed and can only spread when it is not costly, while parasites can maintain especially when resistance is costly (Table 6).

Table 6. Logistic analysis of the presence of the parasite after the introduction of a costly inducible transmission-blocking defence response in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	50.32	<0.0001
Cost of resistance	1	10.20	0.0014
Cost of resistance x Size of the neighbourhood	4	6.78	0.15
Replicate	4	4.33	0,36

3.2.2. Recovery-boosting response ($r_1=0$ and $r_2=1$)

With this type of inducible defence, we observe that the interaction between the cost of resistance and the size of the neighbourhood significantly affects the spread of resistance. To a lesser extent, the size of the neighbourhood also affects the spread of resistance (Table 7).

Table 7. Logistic analysis of the spread (presence/ absence) of a costly inducible recovery-boosting response in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	8.48	0.075
Cost of resistance	1	0.66	0.4183
Cost of resistance x Size of the neighbourhood	4	90.47	<0,0001
Replicate	4	6.59	0.16

Thus, when resistance is associated with a low cost, it is more likely to spread in populations with a low structuration (high sizes of neighbourhood). This trend is reversed in highly structured populations where resistance is then more likely to be maintained when the cost is high. Interestingly, this observed pattern differs from the one observed for the other type of inducible response, i.e. the transmission-blocking one (see § 3.2.1).

This is likely associated with the epidemiological dynamics in such populations, as we observe that parasites persist only for high levels of cost and even more in large neighbourhoods (Table 8) and only when resistance is eliminated. In addition, the lower frequency of resistant uninfected hosts at very high levels of cost and for large neighbourhoods is associated with the higher likelihood of maintenance of the parasite under those circumstances (S2 Figure).

Table 8. Logistic analysis of the presence of the parasite of a costly inducible recovery-boosting response in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	4.96	0.29
Cost of resistance	1	27.96	<0,0001
Cost of resistance x Size of the neighbourhood	4	10.29	0.036
Replicate	1	0.87	0,93

3.2.3. Mixing two inducible defence mechanisms: transmission-blocking and recovery-boosting ($r_1=0$ and $0 < r_2 < 1$)

We now consider the case of a fluctuating investment of the resistant hosts between the two inducible responses, the transmission-blocking and the recovery-boosting one. In other words, this means that r_2 can take values between 0 and 1.

With such mixed strategies, resistance can spread in the population and reach a high frequency for limited values of the cost especially for neighbourhoods of limited size (Figure 2)

Figure 2. Effect the cost and the ratio between 2 components of an inducible resistance having a transmission-blocking and a recovery effect against a pathogen on its spread in different spatial structure and on the parasite prevalence at equilibrium. The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $r_H=0.02$, efficacy of resistance $\text{eff}_1=1$, departure from linearity $m_1=1.4$. The level of investment in the 2 components of the response (r_2) varies between 0 and 1. (Note that this is set of simulations was established with 4 replicates and for 3 levels of neighbourhood).

Given that the two considered inducible defence mechanisms exhibited contrasting patterns of sensitivity to levels of spatial population structure, it is especially

interesting to observe that a strategy mixing these two mechanisms generally favours costly resistance in more highly structured populations (i.e. smaller neighbourhoods). Once the cost of resistance increases, it appears that a ratio biased towards the recovery response is favoured over the transmission-blocking response.

For a small neighbourhood, the cost, the ratio and their interaction are affecting the presence of resistance and an intermediate strategy is the one reaching the highest frequency of resistant hosts when the cost increases (Table 9; Figure 3). For larger neighbourhoods, only the cost and the ratio alone influence the presence of resistance (Table 9) and the selected strategy is the one favouring recovery response (Figure 3).

Table 9: Logistic analysis of the spread (presence/ absence) of a costly inducible response mixing a recovery boosting and a transmission-blocking component in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	2	17.75	0.0001
Ratio between the recovery-boosting and a transmission-blocking components (r2)	1	45.0	<0.0001
Cost of resistance	1	14.54	0.0001
r2 x Cost of resistance	1	17.89	<0.0001
r2 x Size of the neighbourhood	2	94.23	<0.0001
Cost of resistance x Size of the neighbourhood	2	313.24	<0.0001
Cost of resistance x Size of the neighbourhood x r2	2	19.69	<0.0001
replicate	3	1.37	0,71

Figure 3. Effect the cost of an inducible resistance with a transmission-blocking and a recovery component against a pathogen on its spread in different spatial structure. The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $rH=0.02$, efficacy of resistance $eff1=1$, departure from linearity $m1=1.4$. The level of investment in the 2 components of the response (r2) varies between 0 and 1. The categories of the cost are the following ones: low [0-0.25[, medium [0.25-0.5[, high [0.5-0.75[and very high [0.75-1]. (Note that this is set of simulations was established with 4 replicates and for 3 levels of neighbourhood).

3.3. Mixing constitutive and inducible defence strategies ($0 < r_1 < 1$)

We now consider the presence of resistant individuals able to invest in both the constitutive resistance and one of the inducible response, in other words scenarios where $0 < r_1 < 1$.

3.3.1. *Mixing a constitutive and a recovery-boosting response ($0 < r_1 < 1$ and $r_2=1$)*

In this case the host can invest in both a constitutive defence and an inducible response increasing recovery ($r_2=1$). Interestingly the highest values of the frequency of resistance are obtained for an intermediate investment in both responses. While the ratio alone is not significantly affecting the presence of resistance, the size of the neighbourhood and its interaction with the ratio do have a strong impact (Table 9).

Table 9. Logistic analysis of the spread (presence/ absence) of a response with a constitutive component and a recovery-boosting one in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	11.66	0.02
Ratio between the constitutive and the inducible recovery boosting response (r_1)	1	1.25	0.27
$r_1 \times$ Size of the neighbourhood	4	27.14	<0.0001
Replicate	4	0.94	0.92

Thus, for a given ratio, resistance spreads to a higher frequency when the size of the neighbourhood increases, in a similar manner to what was observed with a lone constitutive response (Figure 1). Intermediate values of the ratio allow the spread of resistance as well as the maintenance of the parasite (Figure 4).

Figure 4. Effect of the ratio between a constitutive and an inducible recovery-boosting resistance on the spread of resistance at different sizes of neighbourhood. The graph presents also the parasite presence at equilibrium. The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $r_H=0.02$; departure from linearity $m_1=m_2=1.4$; maximal cost of the constitutive resistance $c_{Max1}=0.1$; maximal cost of the inducible defence $c_{Max2}=0.1$; $ratioEff2=1$.

Values of r_1 close to 1 (corresponding to a higher investment in the constitutive response) permit the spread of resistance only for large neighbourhood sizes without parasite elimination. In other words, when both types of response can occur along a gradient, only the fully transmission-blocking one can become fixed in the population and only a strong investment in it can lead to the eradication of the parasite. If this investment is associated with a fixed cost (due to the constitutive part of the resistance), then resistance is eliminated as well.

3.3.2. Mixing a constitutive and a transmission-blocking response ($0 < r_1 < 1$ and $r_2=0$)

In this scenario, hosts can invest in both a constitutive defence and an inducible response blocking forward transmission ($r_2=0$). As shown in Table 10, both the ratio and its interaction the size of the neighbourhood have an impact on the presence of resistance.

Table 10. Logistic analysis of the spread (presence/ absence) of a response with a constitutive component and a transmission-blocking one in different spatial contexts

Source	d.f.	Log-likelihood χ^2	P-value
Size of the neighbourhood	4	7.06	0.13
Ratio between the constitutive and the inducible transmission blocking response (r_1)	1	22.94	<0.0001
r_1 x Size of the neighbourhood	4	68.23	<0.0001
Replicate	4	2.38	0.67

When the value of r_1 remains below a certain threshold (i.e. a higher investment in the inducible, transmission-blocking response) resistance can spread for the small-size neighbourhood situations and in a very limited number of situations this can lead to the eradication of the parasite. For a higher investment in the constitutive response (higher values of r_1), resistance does not spread except for large neighbourhoods where the parasite is maintained. (S3 Figure).

3.6.3. Mixing all three resistance mechanisms ($0 < r_1 < 1$ and $0 < r_2 < 1$)

Finally we investigate scenarios in which hosts can invest in all three mechanisms of resistance, i.e. cases where both r_1 and r_2 take intermediate values between 0 and 1. We find that the outcome of the simulations (in terms of presence or absence of resistance at the end of a simulation) is primarily affected by the ratios r_1 and r_2 of the investment in the different types of the response, the size of the neighbourhood, and its interaction with r_1 (Table 11).

Table 11. Logistic analysis of the spread (presence/ absence) of a response with a constitutive component, a transmission-blocking and a recovery-boosting response in different spatial contexts.

Source	d.f.	Log-likelihood χ^2	p-value
Size of the neighbourhood	4	63,64	<0.0001 ***
Ratio between the constitutive and the inducible transmission response (r1)	1	40,92	<0.0001 ***
Ratio between the 2 arms of the inducible responses (r2)	1	17,60	<0.0001 ***
r1*r2	1	2,05	0.1519
r1* Size of the neighbourhood	4	145,14	<0.0001 ***
r2* Size of the neighbourhood	4	1,38	0.8484
r1*r2*size of the neighbourhood	4	3.94	0.4144
Replicate	4	0.56	0.9676

For the different sizes of neighbourhood, 3 different outcomes can occur (Figure 6).

Figure 5. Effect of the ratios between the different types of resistance on the spread of resistance and on the parasite prevalence for different sizes of neighbourhood. Each graph represents the average values of the measured parameters, respectively the frequency of resistance and the prevalence.

The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate, $rH=0.02$; departure from linearity $m1=m2=1.4$; maximal cost of the constitutive resistance $cMax1=0.1$; maximal cost of the inducible defence $cMax2=0.1$.

For low values of r1, the fixed cost of resistance is limited and resistance can spread to a high frequency leading to the elimination of the parasite. If there is a minimal investment in the recovery-boosting response, resistance can even fully invade the population and replace the susceptible population. At intermediate values of r1 (approximately $0.1 < r1 < 0.2$) resistance is always lost from the population, in association with the fact that parasites are also lost in nearly all simulations (except when the inducible response is almost strictly affecting transmission). For higher values

of r_1 , while resistance can be maintained in the population, we observe that the frequency of resistance is generally lower in small neighbourhoods. Additionally, in these scenarios, higher values of r_2 appear to be favoured when r_1 is itself higher. In other words, an investment in a recovery-boosting inducible response is favoured when the investment in a constitutive immune response is itself high. In any case, it is interesting to note that, for every neighbourhood size, the highest frequency of resistance was always observed for an intermediate value of r_2 , suggesting that the combination of both inducible defence mechanisms is most advantageous. Finally, we note that at very high values of r_1 , resistance is always lost from the population.

4. Discussion

Host resistance to pathogens can be based on a variety of mechanisms and investment strategies, and the respective selective pressures associated with these different types of resistance can be correspondingly diverse. In this study, we elucidate how these mechanisms of resistance can be differentially selected, not only based on the way the response to a pathogen is mounted (inducible or constitutive resistance), but also based on the specific trait of the host-pathogen interaction affected by this response.

If we consider specifically the scenarios resulting in fixation of resistance (in the sense of 100% of the population being resistant), we observe that such a fixation never occurs for an allele conferring only constitutive resistance, except when no cost is associated with resistance. This corroborates previous theoretical studies dealing with polymorphism of resistance [9, 10] as well as experimental results with plant species infected by rust fungi [11]. The existence of a negative feedback between the prevalence

of resistant hosts and their fitness advantage may indeed limit the evolution of resistance [11, 12].

For the inducible defence, our study shows that fixation can occur not only for a non-costly one but also when the cost remains below a certain threshold. This is valid both for an altruistic and a recovery-boosting resistance. When the resistance is affecting transmission, it can only lead to fixation for small neighbourhood situations for limited values of the cost. When the defence mechanism boosts recovery, fixation can occur at higher costs and for the different sizes of neighbourhood. This is obviously an advantage over a constitutive resistance mechanism. Similarly, one might speculate that transmission-blocking resistance mechanisms, since they do not protect the host from infection, create conditions that are comparatively more detrimental to susceptible competitors, offering an additional benefit. This is reminiscent of comparable effects that have been discussed in the context of the evolution of tolerance [13].

In broad evolutionary terms, the two types of inducible defence considered in this study (increasing recovery and blocking transmission) could be viewed in relative terms as egoist and altruistic strategies respectively. It is beyond the scope of this study and beyond the purpose of this model to draw conclusions about the evolution of altruism from the results presented here, most notably because this model does not keep track of the genetic structure of the population, of relatedness between neighbouring individuals, or of genotypic interactions between hosts and pathogens. Nevertheless, the easy spread of the transmission-blocking response in a small neighbourhood highlights the importance of space in the evolution of altruistic strategies. Such strategies counterselected or selectively neutral in a non-spatial setting, like suicide upon infection [6] can be selected and even become fixed or at least maintained when interactions are limited to their nearest neighbours as shown previously [14] with selection acting

through inclusive fitness benefits for the host. Our results also corroborate previous works where altruistic individuals could be maintained under restricted local interactions despite the evolutionary response of egoists [15].

Importantly, the success of strategies based on a mixture of constitutive and inducible responses (e.g. Figure 5) highlights the possible emergence of a resistance polymorphism, despite the presence on a single parasite (as opposed to a community of parasites infecting the host, which is likely to be the norm in natural systems). In addition, our model does not allow any polymorphism in the parasite population, which could favour cycles of coevolution between hosts and parasites [16, 17]. Moreover, under those conditions where investment is split between these two mechanisms, both resistance and parasitism are maintained in our simulations. Interestingly our work also reveals the possibility that, under certain conditions, a system mixing several resistance alleles can be favoured, and result in both the elimination of the pathogen and the loss of the resistance system itself. Such a system would of course remain open to a later reintroduction of the parasite, as it leaves the host population uninfected and susceptible.

As with any model, whether mathematical or not, our assumptions and equations cannot fully capture the complexity of the epidemiological processes. Our results derive from stochastic simulations and as such they represent a complementary approach to the existing literature that is mostly relying on a combination of analytical and simulation results [5, 6, 14]. While many epidemiological models are formulated in continuous-time, our model is formulated in discrete-time. This approach has received less attention but has been used nonetheless in theoretical studies on the population dynamics of infectious diseases [18], on the evolution of immunity [19] or on disease resistance and tolerance in spatially structured populations [7].

For the sake of simplicity, we have made a number of assumptions that inevitably might be considered artificial compared to a number of natural systems. One such assumption is our choice to have all biological processes operate at the same spatial scale (with the same neighbourhood size) in the model. While this offers the advantage of simplicity, it also corresponds to situations already encountered in theoretical systems [7] as well as in experimental and field studies with species or populations with high or low dispersal. Similarly we have limited the number of parameters in our model with regards to the description of the interaction between hosts and pathogens, and our exploration of the associated parameter spaces. In some cases this was done to focus the analysis, for instance with the parameters associated with the departure from linearity in the cost structure (m_1 and m_2). We chose to restrict the parameter space to a single value for these parameters since preliminary analyses showed no qualitative differences on the outcome of simulations related to a constitutive response. In other cases we had to make arbitrary choices to limit the scope of our exploration. As an example, we chose to have costs of resistance affect host fecundity (as it was presumably more relevant in the context of local density-dependence within a neighbourhood) but we recognize that the dynamics might differ if the costs of resistance were to affect host survival instead.

Another notable point is that we have not been considering any coevolutionary response of the parasite. This would obviously be an important driver of the dynamics of any epidemiological system but this would require adding complexity to this model. The absence of different types or strains of parasites could also be considered as a default in our model as this would probably favour the selection of resistance polymorphism. There is little doubt that the dynamics of resistance would be affected by the presence of parasites harbouring different life-history traits but this would add the complexity of interactions between parasites themselves. Similarly, we have not been

considering the individual variations in infectiousness, whose role in disease emergence has been established [20]. The presence of superspreaders in particular would likely affect the epidemiology and add complexity to the selection of resistance. Such expansions to the model remain to be done in further studies to better understand the co-evolutionary dynamics of host-pathogen systems.

One important caveat specifically associated with our choice of model structure is that the levels of pathogen pressure can vary substantially among our simulations. This could indeed be considered problematic as the infection risk has been shown to favour the constitutive defence mechanism over the inducible one in bacteria [21]. Given our assumptions regarding parasite transmission, the force of infection on an infected host is, on average, higher in larger neighbourhoods. As we believe that it reflects a realistic characteristic of spatially structured populations we chose not to arbitrarily constrain this force of infection, but rather to track prevalence throughout our simulations along with the proportions of sensitive and resistant hosts. Consequently, we did observe some variation in prevalence levels among simulations. This means that the results presented here are driven not only by host-pathogen evolutionary dynamics, but also by host-only evolutionary dynamics in many cases. In other words, these simulations describe the evolution of resistance more at an epidemiological time scale, where wild-type and resistant strategies coexist and compete within a population under a diversity of selective pressures rather than depict the evolution of defence strategies at a true evolutionary time scale.

The epidemiological scale chosen in the current study is nevertheless particularly relevant for many issues regarding host-pathogen interactions and host resistance to disease. The spatial scale of disease transmission is indeed a key factor for the characterization of ongoing epidemics for many diseases e.g. dengue [22-24] or Ebola

[25]. Information regarding this spatial scale is often critically important for decision makers regarding the scope of control measures to adopt in the fight against disease transmission [26-28]. Finally, the spatial aspects of resistance strategies and host population dynamics are likely to be crucial to the outcome of strategies based on the use of genetically modified organisms to combat infectious diseases [29, 30].

To conclude, our approach in this study has been to consider the evolution of various defence strategies, alone or in combination, in a spatial setting. As this model was designed to simulate the dynamics of generic host-parasite interactions, the results presented here should not be seen as practical lessons for any particular host-pathogen system. Nevertheless, this study highlights several essential points for a better understanding of the evolutionary dynamics of such systems. First, it calls for the need to consider spatial interactions to understand the maintenance of costly host defence strategies that potentially could not persist in a non-spatial system. Second, as a corollary, it emphasises how essential it is to better understand the maintenance of polymorphism in resistance mechanisms in natural population and the epidemiological dynamics of host-pathogen interactions.

The results of this study could also be informative for more applied purposes. This approach could indeed be useful in defining the desired characteristics of an engineered resistance that could be used in a pest control strategy relying on an added resistance mechanism [31], which would have to cope with the already existing natural immune responses of the host (e.g. genetically modified mosquitoes able to resist malaria). Moreover, considering an engineered resistance based on a mixed-strategy would have several advantages. First, it should limit the evolution of parasites able to avoid the resistance mechanism. Second, it could permit to get rid of the parasite while simultaneously avoiding the maintenance of an engineered resistance in the population.

Thus in agricultural systems, this could inform about the best strategies for protective measures of plants through the optimization of the use of one or several cultivar resistant to a pathogen (as discussed for example in [32]).

Overall, it appears clearly that taking into account the spatial structure of host-parasite system is essential to better understand the causes that lead to host heterogeneity in nature [33, 34]. Moreover, and as shown previously [34], the contrasting outcomes between various spatial structures are clearly depending on the cost of resistance but also on the type of response against a pathogen. Concerning the question of cost, the existence of a density-dependant reproduction leads to a lower fitness cost in a spatial setting as shown previously [36]. In that context, our results should permit to better understand the spatial, epidemiological and evolutionary dynamics of infectious diseases, while also highlighting the need for further experimental work to elaborate efficient and sustainable strategies for disease management.

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References

1. Gomez P, Buckling A. Bacteria-phage antagonistic coevolution in soil. *Science*. 2011; 332(6025):106-9. doi: 10.1126/science.1198767.
2. Koella JC, Boëte C. A genetic correlation between age at pupation and melanization immune response of the yellow fever mosquito *Aedes aegypti*. *Evolution*. 2002;56(5):1074-9.
3. Moret Y, Schmid-Hempel P. Survival for immunity: the price of immune system activation for bumblebee workers. *Science*. 2000; 290(5494):1166-8.
4. Bergelson J, Purrington CB, Palm CJ, Lopez-Gutierrez JC. Costs of resistance: a test using transgenic *Arabidopsis thaliana*. *Proc Biol Sci*. 1996; 263(1377): 1659-63. doi: 10.1098/rspb.1996.0242.
5. Best A, Webb S, White A, Boots M. Host resistance and coevolution in spatially structured populations. *Proc Biol Sci*. 2011;278 (1715):2216-22. doi: 10.1098/rspb.2010.1978.
6. Débarre F, Lion S, van Baalen M, Gandon S. Evolution of host life-history traits in a spatially structured host-parasite system. *Am Nat*. 2012;179(1):52-63. doi: 10.1086/663199.
7. Horns F, Hood ME. The evolution of disease resistance and tolerance in spatially structured populations. *Ecol Evol*. 2012;2(7):1705-11. doi: 10.1002/ece3.290.
8. Boots M, Best A, Miller MR, White A. The role of ecological feedbacks in the evolution of host defence: what does theory tell us? *Philos Trans R Soc Lond B Biol Sci*. 2009;364(1513):27-36. doi: 10.1098/rstb.2008.0160.
9. Gillespie JH. Natural Selection for Resistance to Epidemics. *Ecology*. 1975;56(2):493-5. doi: 10.2307/1934983.
10. Antonovics J, Thrall PH. The Cost of Resistance and the Maintenance of Genetic Polymorphism in Host-Pathogen Systems. *Proceedings of the Royal Society of London Series B: Biological Sciences*. 1994; 257(1349):105-10. doi: 10.1098/rspb.1994.0101.
11. Roy BA, Kirchner JW. Evolutionary dynamics of pathogen resistance and tolerance. *Evolution*. 2000;54(1):51-63.
12. Carval D, Ferrière R. A unified model for the coevolution of resistance, tolerance, and virulence. *Evolution*. 2010;64(10):2988-3009. doi: 10.1111/j.1558-5646.2010.01035.x.
13. Restif O, Koella JC. Concurrent evolution of resistance and tolerance to pathogens. *Am Nat*. 2004;164(4): E90-102. doi: 10.1086/423713.
14. Lion S, Gandon S. Evolution of spatially structured host-parasite interactions. *J Evol Biol*. 2015;28(1):10-28. doi: 10.1111/jeb.12551.
15. Koella JC. The spatial spread of altruism versus the evolutionary response of egoists. *Proc Biol Sci*. 2000;267(1456):1979-85. doi: 10.1098/rspb.2000.1239.
16. Frank SA. Models of plant-pathogen coevolution. *Trends Genet*. 1992;8(6):213-9.
17. Frank SA. Ecological and genetic models of host-pathogen coevolution. *Heredity (Edinb)*. 1991;67 (Pt 1):73-83.

18. Oli MK, Venkataraman M, Klein PA, Wendland LD, Brown MB. Population dynamics of infectious diseases: A discrete time model. *Ecological Modelling*. 2006;198(1):183-94. doi: <http://dx.doi.org/10.1016/j.ecolmodel.2006.04.007>.
19. van Boven M, Weissing FJ. The evolutionary economics of immunity. *Am Nat*. 2004;163(2):277-94. doi: 10.1086/381407.
20. Lloyd-Smith JO, Schreiber SJ, Kopp PE, Getz WM. Superspreading and the effect of individual variation on disease emergence. *Nature*. 2005; 438 (7066):355-9. doi: 10.1038/nature04153.
21. Westra ER, van Houte S, Oyesiku-Blakemore S, Makin B, Broniewski JM, Best A, et al. Parasite Exposure Drives Selective Evolution of Constitutive versus Inducible Defense. *Curr Biol*. 2015;25(8):1043-9. doi: 10.1016/j.cub.2015.01.065.
22. Aldstadt J, Yoon IK, Tannitisupawong D, Jarman RG, Thomas SJ, Gibbons RV, et al. Space-time analysis of hospitalised dengue patients in rural Thailand reveals important temporal intervals in the pattern of dengue virus transmission. *Trop Med Int Health*. 2012;17(9):1076-85. doi: 10.1111/j.1365-3156.2012.03040.x.
23. Stoddard ST, Forshey BM, Morrison AC, Paz-Soldan VA, Vazquez-Prokopec GM, Astete H, et al. House-to-house human movement drives dengue virus transmission. *Proc Natl Acad Sci U S A*. 2013; 110(3):994-9. doi: 10.1073/pnas.1213349110.
24. Reiner RC, Jr., Stoddard ST, Scott TW. Socially structured human movement shapes dengue transmission despite the diffusive effect of mosquito dispersal. *Epidemics*. 2014;6:30-6. doi: 10.1016/j.epidem.2013.12.003.
25. Merler S, Ajelli M, Fumanelli L, Gomes MF, Piontti AP, Rossi L, et al. Spatiotemporal spread of the 2014 outbreak of Ebola virus disease in Liberia and the effectiveness of non-pharmaceutical interventions: a computational modelling analysis. *Lancet Infect Dis*. 2015;15(2):204-11. doi: 10.1016/S1473-3099(14)71074-6.
26. Ferguson NM, Donnelly CA, Anderson RM. The foot-and-mouth epidemic in Great Britain: pattern of spread and impact of interventions. *Science*. 2001;292(5519):1155-60. doi: 10.1126/science.1061020.
27. Keeling MJ, Woolhouse ME, May RM, Davies G, Grenfell BT. Modelling vaccination strategies against foot-and-mouth disease. *Nature*. 2003;421(6919):136-42. doi: 10.1038/nature01343.
28. Tildesley MJ, Savill NJ, Shaw DJ, Deardon R, Brooks SP, Woolhouse ME, et al. Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK. *Nature*. 2006;440(7080):83-6. doi: 10.1038/nature04324.
29. Kiszewski AE, Spielman A. Spatially explicit model of transposon-based genetic drive mechanisms for displacing fluctuating populations of anopheline vector mosquitoes. *J Med Entomol*. 1998;35(4):584-90.
30. Huang Y, Lloyd AL, Legros M, Gould F. Gene-drive into insect populations with age and spatial structure: a theoretical assessment. *Evol Appl*. 2011; 4(3):415-28. doi: 10.1111/j.1752-4571.2010.00153.x.
31. Gantz, V. M., Jasinskiene, N., Tatarenkova, O., Fazekas, A., Macias, V. M., Bier, E. and James, A. A. (2015) Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito, *Anopheles stephensi*. *Proc.Natl. Acad. Sci. USA* 112(49):E6736-43

32. Fabre F., Rousseau E, Mailleret L, Moury B. Durable strategies to deploy plant resistance in agricultural landscapes. *New Phytol.* 2012. 193(4):1064-75. doi: 10.1111/j.1469-8137.2011.04019.x.
33. Laine AL, Burdon JJ, Dodds PN, Thrall PH. Spatial variation in disease resistance: from molecules to metapopulations. *J Ecol.* 2011; 99(1):96-112. doi: 10.1111/j.1365-2745.2010.01738.x.
34. Penczykowski RM, Laine AL, Koskella B. Understanding the ecology and evolution of host-parasite interactions across scales. *Evol Appl.* 2016; 9(1):37-52. doi: 10.1111/eva.12294.
35. Ashby B, Gupta S, Buckling A. Spatial structure mitigates fitness costs in host-parasite coevolution. *Am Nat.* 2014;183(3):E64-74. doi: 10.1086/674826.
36. Débarre F. Fitness costs in spatially structured environments. *Evolution.* 2015;69(5):1329-35. doi: 10.1111/evo.12646.

Supporting information

S1 Figure. Effect of the fitness cost of resistance and of the size of neighbourhood on the spread of a transmission-blocking resistance against a pathogen and on the parasite presence at equilibrium.

The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $rH=0.02$, efficacy of resistance $\text{eff2}=1$, departure from linearity $m2=1.4$, level of investment in the constitutive resistance $\text{ratio1}=0$, level of investment in the recovery resistance $\text{ratio2}=0$.

S2 Figure. Effect of the fitness cost of resistance and of the size of neighbourhood on the spread of a resistance increasing recovery against a pathogen and on the parasite presence at equilibrium.

The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate $rH=0.02$, efficacy of resistance $\text{eff2}=1$; departure from linearity $m2=1.4$, level of investment in the constitutive resistance $\text{ratio1}=0$; level of investment in the recovery-boosting resistance $\text{ratio2}=0.5$.

S3 Figure. Effect of the ratio between a constitutive and an inducible transmission-blocking resistance on the spread of resistance at different sizes of neighbourhood. The graph presents also the parasite presence at equilibrium.

The parameters are the following ones: transmission rate $\beta=0.25$, virulence of the pathogen $\alpha=0.25$, mortality $\mu=0.01$, recovery rate $\gamma=0.1$, reproduction rate, $rH=0.02$; departure from linearity $m1=m2=1.4$; maximal cost of the constitutive resistance $c\text{Max1}=0.1$; maximal cost of the inducible defence $c\text{Max2}=0.1$; $\text{ratioEff2}=0$.

801
802

Size of the neighbourhood

Presence of the Parasite

Size of the neighbourhood = 1

Size of the neighbourhood = 3

Size of the neighbourhood = 5

Cost of the inducible resistance

The viridis colorscale represents the level of the frequency of resistance for the graph on the left side and the prevalence of the parasite for the graph on the right side.

Size of the neighbourhood = 1

Size of the neighbourhood = 3

Size of the neighbourhood = 5

ratio between the transmission-blocking and the recovery components of the inducible response

Ratio between a constitutive response and an inducible recovery response

Size of the neighbourhood

Presence of the Parasite

1

2

3

4

5

Size of the neighbourhood = 1

Size of the neighbourhood = 3

Size of the neighbourhood = 5

Ratio between the constitutive resistance and the inducible response

The viridis colorscale represents the level of the frequency of resistance for the graph on the left side and the prevalence of the parasite for the graph on the right side.