Title: Evolution of behavioral resistance in host-pathogen systems

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Abstract

Behavioral resistance to parasites is widespread in animals, yet little is known about the evolutionary dynamics that have shaped these strategies. Theory developed for the evolution of physiological parasite resistance can only be applied to behavioral resistance under limited circumstances. We find that accounting explicitly for the behavioral processes, including the detectability of infected individuals, leads to novel dynamics that are strongly dependent on the nature of the costs and benefits of social interactions. As with physiological resistance, the evolutionary dynamics can also lead to mixed strategies that balance the costs of disease risk and the benefits of social interaction, with implications for understanding avoidance strategies in human disease outbreaks.

Introduction

Hosts resist parasites using diverse strategies, with broad implications for host-parasite coevolution [1–4]. Previous theoretical models of resistance evolution have largely focused on physiological or biochemical resistance [1,5–7]. Yet resistance against parasites can also take the form of behavioral traits [3,8,9] such as direct avoidance or "disgust" in response to diseased individuals [10,11] or general avoidance of interactions with other individuals, which in a human context is now termed "social distancing." Here, we ask whether the ecological and evolutionary dynamics of behavioral defenses against parasites operate according to similar principles as physiological defenses.

Host behavior is implicit in classical models of microparasite transmission as a component of the parameter β [12,13]. β is a composite of multiple factors [14], including, for directly transmitted parasites, the contact rate between hosts, which is a function of host behavior, and the per contact transmission probability, which is a function of host physiology [15]. Models of resistance evolution typically vary the per contact transmission probability, i.e. the physiological resistance [5,16]. Nevertheless, a high degree of variation in behavioral resistance to parasites has been reported across and within species: for example, avoidance of infected conspecifics in crustaceans [17], birds [18,19], and primates [20], including humans [10]. Despite the broad diversity of these behaviors [8,21,22], behavioral resistance has rarely been examined explicitly in theoretical contexts [23,24]. It remains unknown whether evolutionary dynamics of behavioral resistance follow the same patterns as physiological resistance. Previous theoretical research on physiological resistance has shown that susceptible and resistant individuals can coexist in the presence of a disease when resistance carries a direct

46 physiological cost [5,7,25], but such models have also not considered how behavioral costs
47 might influence resistance evolution.

48 Here, we develop a theoretical model of a disease that is transmitted in a social context,
49 through direct contact or aerosol, and investigate the evolution of behavioral resistance under
50 several assumptions about behavioral processes and cost-benefit trade-offs. We show that
51 behavioral resistance can result in evolutionary dynamics that are different from physiological
52 resistance, depending on the specificity of behavioral responses to diseased conspecifics and the
53 nature of the costs and benefits of sociality.

54

55 **The Model**

56 *Social Behavior*

57 We model the social behavior of the host in a population of individuals that enter into groups or
58 remain singletons. Let S be the number of singletons and G the number of groups of size T, and
59 total population size, $N = S + TG$.

60 The frequency of groups depends on the group encounter rate, ρ, and group dissociation
61 rate, υ. We use the simplest case of pair formation ($T = 2$) to illustrate the dynamics. Pair
62 formation in populations has been studied in the context of mating and marriage, and represents a
63 complex problem of sampling without replacement [26,27]. Following previous work [28], we
64 consider two forms of encounter. First, singletons can encounter one another at a constant
65 frequency that is independent of their density, as would occur when individuals seek others out
66 to form associations. Second, singletons can encounter others randomly, such that encounters
67 occur at a higher rate at greater densities. These two types of group formation have parallels with

68 frequency-dependent and density-dependent disease transmission processes [28,29]. Throughout,
69 the derivations of the equations are given in the Supplementary Materials (S1).

70 *Equilibrium Group Formation*

71 The number of groups at equilibrium under frequency-dependent encounter is

$$G = \left(\frac{\frac{\rho}{\upsilon}}{1 + \frac{\rho}{\upsilon}} \right) \left(\frac{N}{T} \right) \tag{1}$$

72 In the case of density dependent encounter, we assume the rate of group formation is a
73 linear function of the number of singletons, πS, rather than the total population density. Then, the
74 number of groups at equilibrium is

$$G = N - \frac{\left(-\upsilon + \sqrt{\upsilon^2 + 4T\rho\upsilon N} \right)}{2T^2\rho} \tag{2}$$

75

76 *Behavioral Resistance*

77 We compare two types of behavioral resistance: specific avoidance of diseased individuals and
78 general avoidance of all associations. For specific avoidance, a healthy, avoiding individual can
79 detect an infected individual, and avoid pairing with it, determined by a factor ϕ. For general
80 avoidance, a healthy, avoiding individual encounters all other individuals, regardless of their
81 infection status, at a reduced rate $(\rho - a)$, relative to the background rate of non-avoiding
82 individuals ρ. We derive how R_0 depends on the equilibrium frequency of pairs.

83

84 *Evolution of Behavioral Resistance*

85 To understand the evolution of behavioral resistance we use the one-locus, two allele dynamical
86 framework developed for physiological resistance evolution [5]. In this system, X_1 and X_2

represent two haploid genotypes that differ in their behavioral resistance to the disease, with X_2 being the avoider. X_1 and X_2 are equivalent in their transmission once infected, such that they can be pooled into one class of diseased individuals, Y. Transmission occurs at rate δ from infected (Y) individuals to X_1 or X_2 when they are in a pair. Individuals can enter into a pair with their own type and the other types, the number of pairs of each type calculated from binomial proportions. We use b and $(b-c)$ to refer to birth rate for X_1 and X_2 respectively, where c is the cost of resistance (see below), and μ the background mortality rate. We assume the disease is sterilizing, such that diseased individuals do not contribute to reproduction. We also impose density dependence on birth rate of the healthy individuals because without a numerical or ecological feedback, the system does not reach stable equilibrium [25]. These processes are represented by

$$\frac{dX_1}{dt} = X_1(b - kN - \mu) - \delta\left(\frac{2GX_1Y}{N^2}\right) \quad (3)$$

$$\frac{dX_2}{dt} = X_2((b-c) - kN - \mu) - \delta\left(\frac{2GX_2Y}{N^2}\right) \quad (4)$$

$$\frac{dY}{dt} = \delta\left(\frac{2GY}{N^2}\right)(X_1 + X_2) - \mu Y \quad (5)$$

We simulated each model to equilibrium using an ordinary differential equation solver (function "ode" Runge-Kutta "rk4" method) from the R package *deSolve* [29,30]. We explored a range of values for each parameter (see results), and confirmed equilibria by perturbation.

Resistance Costs

Physiological resistance is usually assumed to carry some cost that results in reduced fitness in the absence of the parasite [5,25]. Similarly, we assume X_2 individuals pay some reproductive cost for avoiding others. First, avoidance may be costly regardless of whether it is instantiated;

for example, a less active genotype could have fewer encounters with others, but also have reduced food acquisition. Thus, the birth rate of X_2 is $(b - c)$.

Alternatively, costs of avoidance may only be instantiated when the individual avoids being in a group. This reflects a situation where sociality is beneficial. Thus, we examine the case in which the reproduction of both X_1 and X_2 increases as a function of the frequency at which it pairs. We model this benefit as a direct, linear function of the frequency of pairs within each genotype, such that birth rate for X_1 is calculated as $(1 + \frac{TG_{X1}}{X_1})b_1$ and for X_2 as $\left(1 + \frac{TG_{X2}}{X_2}\right)b_2$.

Results

Overall Dynamics

In basic models of physiological resistance, the transmission coefficient is a compound of per contact transmission rate and number of contacts. It can be shown that if all individuals are in pairs, i.e. in contact, then the dynamics of disease with pair formation are identical to the physiological resistance model.

If pair formation is incomplete, the basic reproductive number of the parasite, $R_0 = \frac{2\delta G}{N\mu}$, and equivalent to canonical formulations for R_0. We first examined the effect of the different pairing behaviors and avoidance strategies on the equilibrium frequency of individuals in pairs, prevalence of disease, and R_0 when only X_2, the avoiding genotype, was present (Fig. 1).

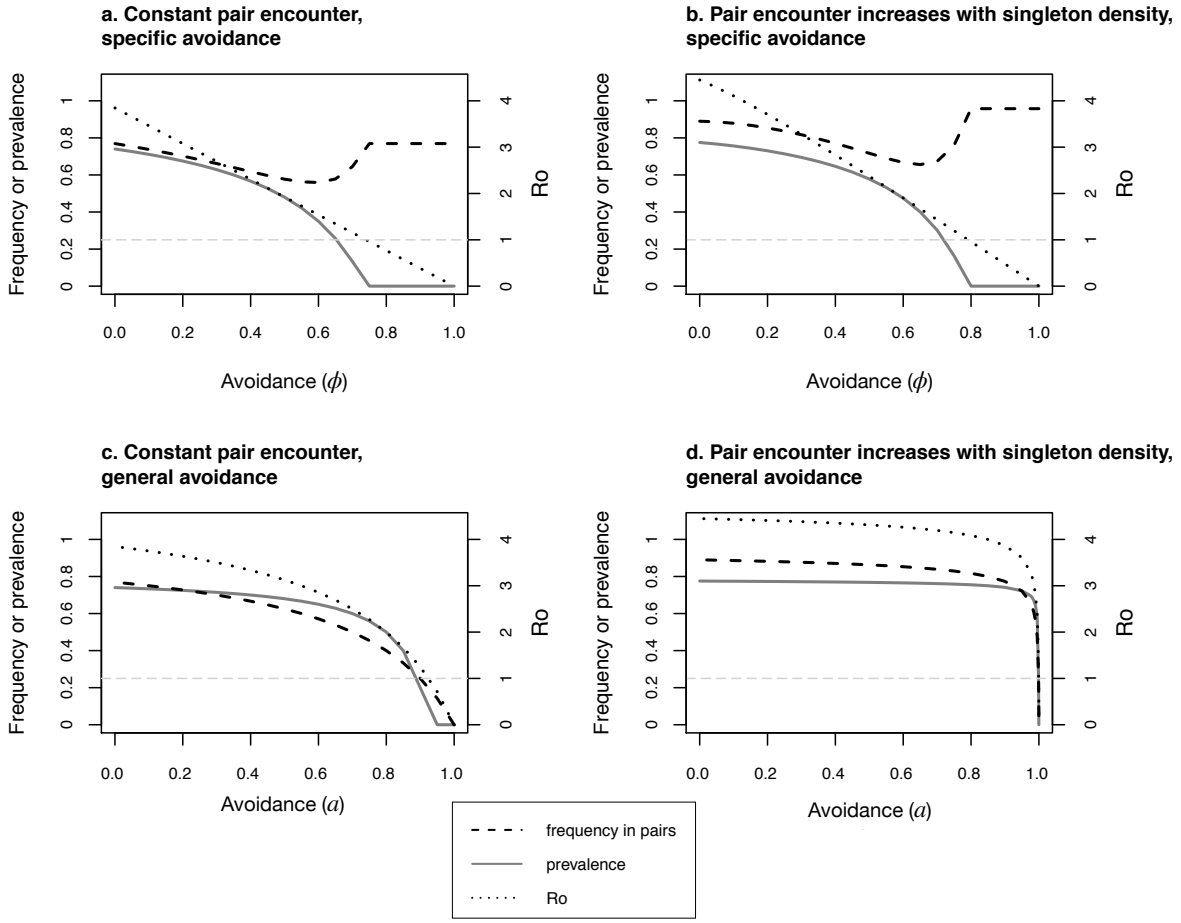


Figure 1. Pairing and disease dynamics at equilibrium when only the avoiding genotype (X_2) is present in the population, under different pairing processes and avoidance strategies. The light gray horizontal dotted line represents when the basic reproductive number, $R_0 = 1$, below which the disease cannot persist in the population, and above which sustained transmission is possible. $b = 1, \mu = 0.2, \delta = 1, \upsilon = 0.3, k = 0.01$.

Under both pair formation processes, increased specific avoidance of infected individuals (Figs. 1a and 1b) is highly effective at reducing prevalence of the disease, and as X_2 avoids Y it also results in a decrease in the frequency of individuals in pairs. However, the frequency of individuals in pairs increases again at high specific avoidance, because few infected individuals remain for the healthy X_2 individuals to encounter. With further avoidance, R_0 falls below 1,

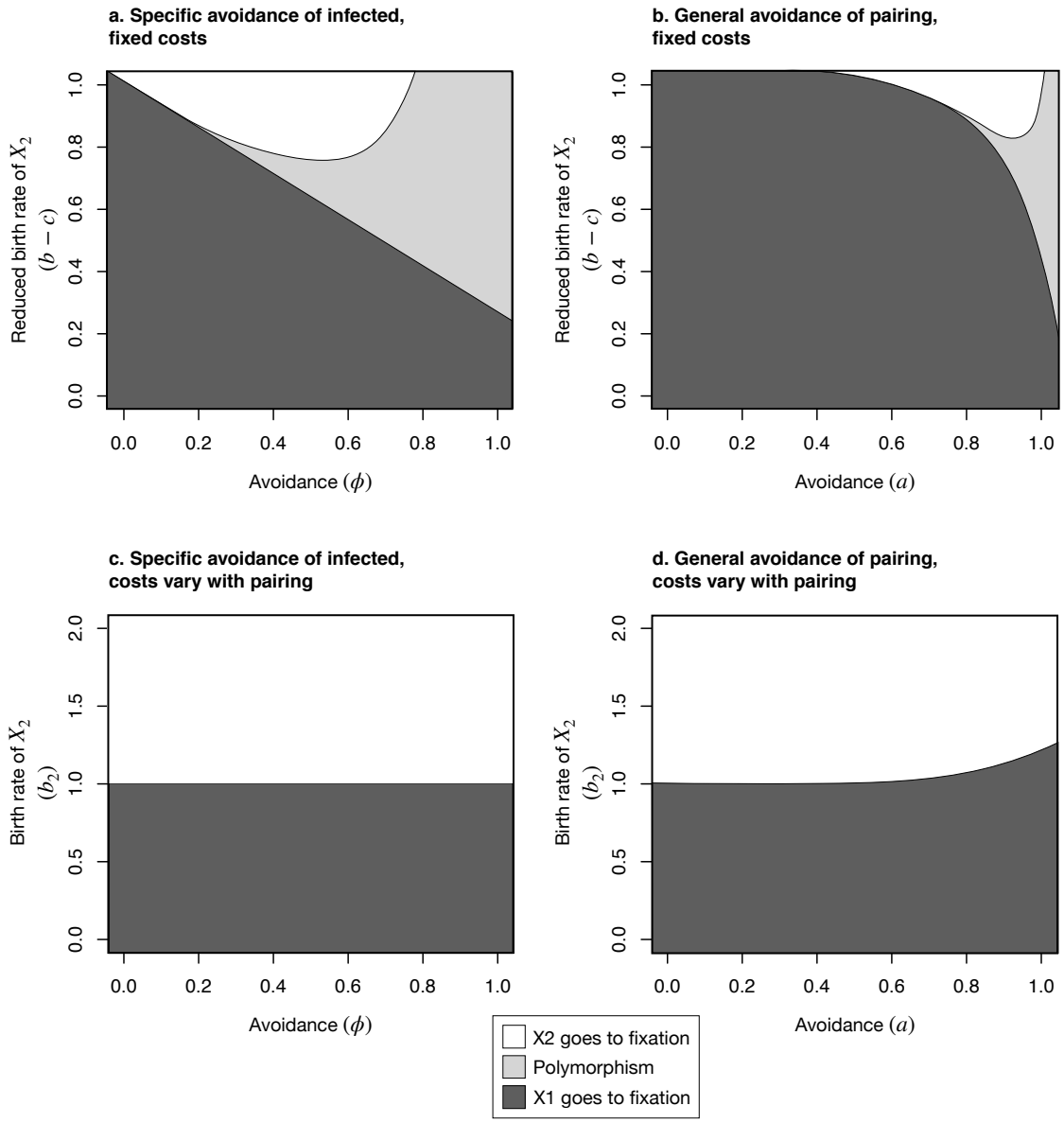
prevalence drops to 0, and pair formation is only among healthy individuals. Thus, at high levels of specific avoidance, hosts can successfully extirpate the disease from the population while maintaining their social structure.

Contrarily, while general avoidance reduces R_0 and prevalence, as long as per contact transmission rate is high, avoidance of pairing must be nearly complete (Figs. 1c and 1d) to reduce R_0 below the threshold of 1. In other words, if hosts are not able to detect infection in conspecifics, behavioral avoidance effectively reduces disease risk, but possibly at levels where the hosts compromise their social structure.

Resistance Evolution

We next examined the evolutionary dynamics in a population with genetic variants that do (X_2) and do not (X_1) avoid disease when resistance carried a fixed cost. When behavioral resistance was through specific avoidance of infected individuals (ϕ), X_1 and X_2 could stably coexist across a range of avoidance levels, even at very high costs (>50% reduction in birth rate) when avoidance of infected individuals was highest (Fig. 2a). Varying behavioral resistance through general avoidance, ($\rho - a$), resulted in the same overall pattern, with polymorphism occurring across the broadest range of costs when avoidance was greatest (Fig. 2b). However, consistent with the results in Fig. 1, even high levels of general avoidance still resulted in some frequency of pairing with infected individuals. Thus, under the general avoidance strategy, X_2 could not tolerate as great a reduction in birth rate at intermediate levels of avoidance.

158



159 **Figure 2:** Shaded areas represent equilibrium gene frequency states for the models when the cost of X_2 and the
160 avoidance strategy of X_2 are varied. Possible outcomes include X_1 or X_2 becoming fixed in the population, or X_1 and
161 X_2 coexisting, i.e. polymorphism. All plots show results for constant rate of pair encounter. (Corresponding plots for
162 density-dependent pair encounter rates can be found in Supplementary Materials S2). $b = 1, \mu = 0.2, \delta = 1, \upsilon =$
163 $0.3, k = 0.01$.
164

165 We next assumed that individuals receive a benefit as a function of social behavior

166 relative to being alone, we found that in the case of specific avoidance the benefits of reduced

disease risk evenly balanced the costs of lost social interactions, such that X_2 only went to fixation when its fitness was relatively greater than X_1 (Fig. 2c). When avoidance was general, X_1 could even sometimes reach fixation when X_2 had a higher birth rate, because at high rates of general avoidance, reductions in disease risk are not substantial enough to compensate for the loss of social contacts (Fig. 2d). In both cases, when costs were linearly dependent on the frequency of individuals in pairs, polymorphism between X_1 and X_2 was not possible.

While we only present the results from models with a constant rate of pair encounter, the patterns of polymorphism were qualitatively similar when pair encounter rate depended on the density of singletons (Supplementary Materials S2).

Discussion

We present evidence here that the evolution of behavioral resistance can differ from physiological or biochemical resistance evolution depending on the costs and benefits of resistance and sociality. Similar to physiological resistance, polymorphism in behavioral resistance can be maintained across a broad range of fixed costs when the level of resistance is high [5,25]. When enough behaviorally resistant individuals are present in the population, behavioral avoidance strategies can effectively reduce the disease risk so that susceptible individuals can coexist.

However, such polymorphism is much less likely to occur when social interactions have benefits, as they do in many social organisms. In the case of specific avoidance, when infected individuals are detectable, social interactions are limited only in situations where avoidance will provide the benefit of reduced transmission. Thus specific avoidance reduces the negative impacts of lost social opportunities, and even allows for the full recuperation of social behavior

when avoidance is high enough to fully extirpate the disease through behavioral mechanisms. Yet when avoidance is general and at a high level, the costs of lost social interactions are higher than the benefits of reduced disease risk because of 'mistakes' in selection of diseased or healthy social partners. This comparison highlights the challenge of controlling an outbreak of an emergent disease, especially when asymptomatic transmission is possible, as in COVID-19 [31]. The maintenance of a polymorphic state under some conditions suggests that if avoidance behavior could be performed flexibly, a mixed strategy of social distancing that allows for some social interaction could strike a balance between the costs and benefits.

To dissect the basic differences between behavioral and physiological resistance we have deliberately kept the models simple. Application to any specific host-pathogen context would require more complexity in the temporal and social structure of the interactions. For example, in nature individuals interact more fluidly, increasing opportunities for transmission. As groups become larger, transmission within groups and movement between groups would be possible, and behavioral resistance strategies could become more diverse. Consistent with previous research, this simple model highlights trade-offs between the benefits of reducing disease risk and the costs of foregoing other opportunities, whether nutritional [23], reproductive [24], or in the case of our model, social.

Behavioral and physiological resistance are not separate phenomena but are likely to interact, with behavioral effects being antecedent to physiological resistance, in a framework similar to a two-step infection process [32]. In such situations, genetic associations can arise between genes determining resistance, even though they may have no direct physiological interaction. Physiological and behavioral defenses against parasites might therefore trade-off

with one another either directly or indirectly. For example, house finches that avoid sick conspecifics invest less in immune defenses [19].

A genetic basis for parasite avoidance behaviors has support from knockout experiments in laboratory mice [33] and selective breeding in livestock [34]. Direct evidence of genetic polymorphism in social behavior in natural populations has also begun to emerge [35]. Behavioral resistance can thus be innate, as we model it, or it can be learned through prior exposure [36–38], and how dynamics of learned resistance would differ from innate is a rich direction for future research. Together these innate and learned responses represent a suite of psychological and cognitive mechanisms that psychologists have termed the "behavioral immune system" [39]. Innate and acquired behavioral resistance are conceptually parallel to innate and adaptive immune responses, but whether this metaphor translates to equivalent dynamics merits further examination.

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Code and Supporting Materials

All code and derivations can be found in the Supplementary Materials.

Competing Interests

The authors have no competing interests to declare.

Authors' Contributions

CRA and JA conceived the project and derived the equations together. CRA carried out the simulations and drafted the manuscript. JA provided critical input on the simulations and revisions to the manuscript. All authors gave final approval for publication and agree to be held accountable for the work performed therein.

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Supplementary Materials – S1: Equations
Equations are numbered as Supplementary Equations (SE) for ease of reference relative to the equations in the main text.

If encounter rate is at a constant frequency
The differential equations for number of groups and singletons are given as:

$$\frac{dG}{dt} = \rho S - \upsilon G \qquad (SE1)$$

$$\frac{dS}{dt} = T(\upsilon G - \rho S) \qquad (SE2)$$

By setting $\frac{dS}{dt}$ and $\frac{dG}{dt}$ to zero, we can calculate that at equilibrium, the ratio of groups to singletons, $\frac{G}{S} = \frac{\rho}{\upsilon}$. The frequency of individuals in groups, or $\frac{TG}{N}$, can be calculated from this equation as $\frac{\frac{\rho}{\upsilon}}{1+\frac{\rho}{\upsilon}}$. Thus, the number of groups at equilibrium is

Number of pairs of X1 (if all the individuals in the population were X1):

$$G_1 = \left(\frac{\frac{\rho}{\upsilon}}{1+\frac{\rho}{\upsilon}}\right)\left(\frac{N}{T}\right) \qquad (SE3)$$

Number of pairs of X2 (if all individuals in the population were X2):

$$G_2 = \left(\frac{\frac{\rho - a}{\upsilon}}{1+\frac{\rho - a}{\upsilon}}\right)\left(\frac{N}{T}\right) \qquad (SE4)$$

If encounter rate is dependent on the density of singletons
Such a scenario could be represented by a number of functions, but for the sake of simplicity, we calculate the rate at which groups encounter one another as a function of the number of singletons, ρS. Thus, as more singletons exist in the population, group formation increases.

This gives us the following differential equations:

$$\frac{dG}{dt} = \rho S^2 - \upsilon G \qquad (SE5)$$

$$\frac{dS}{dt} = T(\upsilon G - \rho S^2) \qquad (SE6)$$

At equilibrium, $\frac{G}{S^2} = \frac{\rho}{\upsilon}$. We can substitute $G = \frac{N-S}{T}$ into this equation, which can be reduced to $T\rho S^2 + \upsilon S - \upsilon N = 0$. Using the quadratic formula, we can calculate that

$$S = \frac{-\mu + \sqrt{\mu^2 + 4T\rho\mu N}}{2T\rho} \qquad (SE7)$$

And the number of pairs at equilibrium can be calculated as follows.

$$G = \frac{N - S}{T} \qquad (SE8)$$

Thus, the number of pairs of X1 (if all the individuals in the population were X1) is

$$G_1 = N - \frac{-\upsilon + \sqrt{\upsilon^2 + 4T(\rho)\upsilon N}}{2T^2\rho} \qquad (SE9)$$

And the number of pairs of X2 (if all individuals in the population were X2) is

$$G_2 = N - \frac{-\upsilon + \sqrt{\upsilon^2 + 4T(\rho - a)\upsilon N}}{2T^2(\rho - a)} \qquad (SE10)$$

Where…
N = total population size
ρ = rate of pair encounter
υ = rate of unpairing
a = general avoidance parameter (=0 in case of specific avoidance)
T = group size (=2 henceforth)

Number of pairs of each type
Number of pairs of X1 and X2 with Y individuals, which provides the opportunity for transmission:

$$P_{X1Y} = 2G_1\left(\frac{X_1}{N}\right)\left(\frac{Y}{N}\right) = \left(\frac{2G_1X_1Y}{N^2}\right) \qquad (SE11)$$

$$P_{X2Y} = (1-\phi)\,2G_2\left(\frac{X_2}{N}\right)\left(\frac{Y}{N}\right) = (1-\phi)\left(\frac{2G_2X_2Y}{N^2}\right) \qquad (SE12)$$

Where ϕ = specific avoidance (=0 in case of general avoidance)

Total number of X1 and X2 in pairs:

$$P_{X1} = \frac{2G_1X_1}{N} \quad (SE13)$$

$$P_{X2} = \frac{2G_2X_2}{N} - (\phi)\, 2G_2\left(\frac{X_2}{N}\right)\left(\frac{Y}{N}\right) \quad (SE14)$$

where subtracting $(\phi)\, 2G_2\left(\frac{X_2}{N}\right)\left(\frac{Y}{N}\right)$ represents removing the pairs that were NOT formed as a result of specific avoidance of infected individuals.

Fixed costs

If costs are fixed, then the following equations define the rate of change of each type of individual:

$$\frac{dX_1}{dt} = X_1(b - kN - \mu) - \delta\left(\frac{2G_1X_1Y}{N^2}\right) \quad (SE15)$$

$$\frac{dX_2}{dt} = X_2((b - c) - kN - \mu) - \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) \quad (SE16)$$

$$\frac{dY}{dt} = \delta\left(\frac{2G_1X_1Y}{N^2}\right) + \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) - \mu Y \quad (SE17)$$

Where…
b = birth rate
c = fixed cost
δ = transmission given contact
μ = mortality

Costs depend on social structure

If costs depend on pairing, then the following equations define the rate of change of each type of individual:

$$\frac{dX_1}{dt} = X_1\left(b_1\left(1 + \frac{P_{X1}}{X_1}\right) - kN - \mu\right) - \delta\left(\frac{2G_1X_1Y}{N^2}\right) \quad (SE18)$$

$$\frac{dX_2}{dt} = X_2\left((b_2\left(1 + \frac{P_{X2}}{X_2}\right) - kN - \mu\right) - \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) \quad (SE19)$$

$$\frac{dY}{dt} = \delta\left(\frac{2G_1X_1Y}{N^2}\right) + \delta(1 - \phi)\left(\frac{2G_2X_2Y}{N^2}\right) - \mu Y \quad (SE20)$$

Transmission term in behavioral vs. physiological resistance

When all individuals are in pairs, the model of behavioral processes of resistance is identical to a mass action model of mixing behavior. To illustrate this, using the X_1 genotype as an example,

the transmission term is classically represented by $\beta X_1 \left(\frac{Y}{N}\right)$. In the present behavioral model, when all individuals are in pairs, $G = \frac{N}{2}$. Substituting this fraction for G in the transmission term for X_1 above gives

$$2\delta \left(\frac{N}{2}\right)\left(\frac{X_1}{N}\right)\left(\frac{Y}{N}\right) \quad (SE21)$$

which simplifies to the equivalent $\delta X_1 \left(\frac{Y}{N}\right)$. The same follows for transmission to X_2.

Calculating R_0

R_0, or the basic reproductive number, is the condition that must be met for new infections to be produced in any time step of the model. In other words, the differential equation for Y must be greater than 0.

$$0 < \frac{dY}{dt} = \frac{2\delta GY}{N^2}(X_1 + X_2) - \mu Y \quad (SE22)$$

When Y is rare, $X_1 + X_2 \approx N$, which gives

$$0 < \frac{2\delta G}{N} - \mu \quad (SE23)$$

This can be further reduced to the formula for R_0:

$$1 < \frac{2\delta G}{N\mu} = R_0 \quad (SE24)$$

This formulation represents the frequency of pairs $\frac{2G}{N}$ multiplied by per contact transmission probability (δ), divided by the background mortality rate (μ).

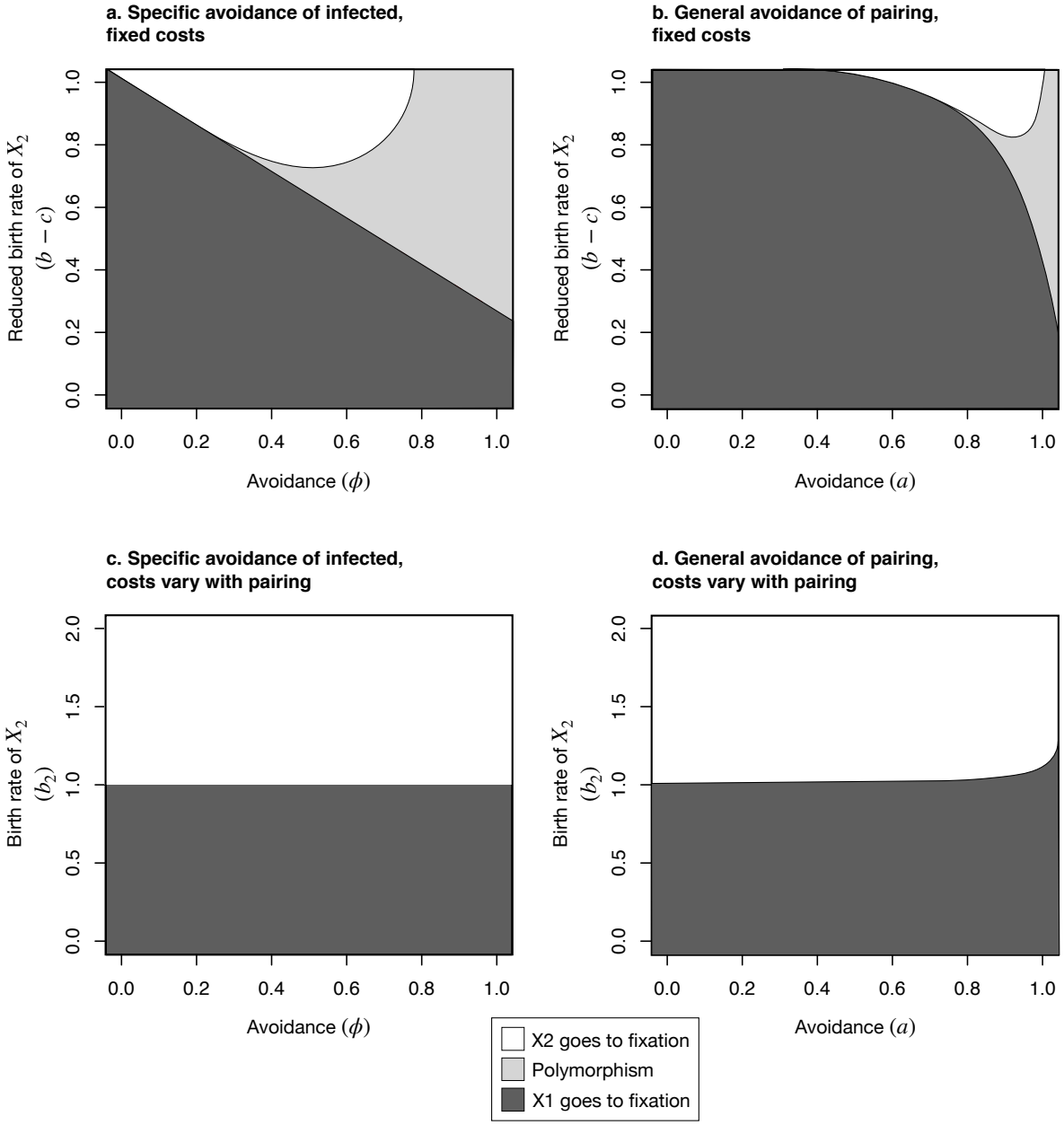

Figure S1: Shaded areas represent equilibrium gene frequency states for the models when the cost of X_2 and the avoidance strategy of X_2 are varied. Possible outcomes include X_1 or X_2 becoming fixed in the population, or X_1 and X_2 coexisting, i.e. polymorphism. All plots show results for density dependent encounter rate. $b = 1, \mu = 0.2, \delta = 1, \upsilon = 0.3, k = 0.01$.