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ORIGINAL PAPER

The evolution of mutualism from reciprocal parasitism: more ecological clothes for the Prisoner's Dilemma

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Abstract Many mutualisms involve reciprocal exploitation, such that each species in a mutualism is a consumer of a resource provided by the other. Frequently, such mutualisms are reformed each generation, and where they involve close physiological contact, such as between mycorrhizal fungi and plants, they can be considered as examples of reciprocal parasitism. Here we place such interactions in the framework of the Prisoner's Dilemma, and examine the conditions for the spread of mutualism using a population genetics model analogous to that used for understanding the genetic and numerical dynamics of host-parasite interactions. Genetic variants within each of two species determine whether the interaction is mutualistic or selfish, the latter being represented by resistance to being exploited or parasitized. We assume that there are fitness costs to resistance which are present even in the absence of the interaction. Just as in host-parasite interactions, we examine the effect of assuming that encounter rates between potential mutualists (and therefore entry into the Prisoner's Dilemma 'game') depend on the density and frequency of the different types interacting individuals. These elements of ecological realism greatly facilitate the evolution of mutualism even in the absence of spatial structure or iterative encounters. Moreover, stable genetic polymorphisms for resistant (selfish) and susceptible (mutualistic) alleles can be maintained, something that is not possible with the classical Prisoner's Dilemma formulation. The sensitivity of the outcomes to levels of density-dependence and mortality rate suggests environmental as well as genetic processes are likely to be important in determining directions in this pathway to mutualism.

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Introduction

> *Mutualisms are best viewed as reciprocally exploitative interactions that provide net benefits to both partner species*
> Bronstein (2001)

The evolution of mutualisms has long attracted the attention of biologists, especially because of the dilemma, recognized by Darwin (1859, p. 201), that in nature we often see traits that appear to be there for the specific benefit of another species, "for such could not have been produced by natural selection". It is now generally accepted that most mutualisms involve some form of exploitation (Bronstein 2001), where a resource provided by one species is consumed by another. In many mutualisms, such resource-consumer interactions are reciprocal or bi-directional with each species functioning both as a consumer and as a resource (Holland and DeAngelis 2010). Resources may be nutrition based (as with mycorrhizal fungi and plants; Hacskaylo 1972) or may involve transportation (plants and their pollinators; Heinrich and Raven 1972) or protection (ants and acacias; Janzen 1966). Where such interactions re-associate each generation (i.e. there is no co-transmission of the interacting species), and involve physiological exchange of resources, they can be considered as examples of reciprocal or bi-directional exploitation or parasitism. In this paper, we therefore use a host-parasite framework to analyse the outcome of such situations. Examples of reciprocal exploitation are legion, even in classical mutualistic systems (Irwin et al. 2010; Kiers et al. 2010), and a direct parasitic origin is posited for some (Wang and Wu 2014).

At an abstract, heuristic level, mutualism based on reciprocal exploitation has been conceptualized by the metaphor of "The Prisoner's Dilemma". This metaphor describes the situation where two prisoners stand to gain by jointly co-operating in denying a crime, yet where each individual gains even more if they deny the crime and implicate the other individual. In the absence of information about what the other prisoner is going to do, it seems always better to implicate the other individual. How this "Prisoner's Dilemma" can be overcome, and therefore how mutualism can be favoured, has been the subject of numerous studies by evolutionary biologists, sociologists and economists, not always without controversy (Herre et al. 1999; Nowak 2006; West et al. 2011; Lewis and Dumbrell 2013).

These studies have shown that evolution of mutualism is favoured if two ecologically likely circumstances are present, namely differential association among individuals and repeated encounters. Differential association may be the result of spatial or kin substructuring (e.g. from limited dispersal), co-inheritance (e.g. through maternal transmission) or chance effects (e.g. in small populations). Repeated or iterative encounters also favour the evolution of mutualism, and include interactions such as "tit for tat" that need not involve learning (but see Scheuring 2005), while others such as punishment for non-mutualistic actions usually involve trait or actor recognition and actions dependent on prior outcomes (Jansen and van Baalen 2006; Fehr and Gächter 2002).

In this paper, we ask how adding another element of ecological realism, namely the fact that encounters between potential mutualists (and therefore entry into the Prisoner's Dilemma 'game') are likely to depend on the density and frequency of the interacting species, alter the conditions for the evolution of mutualism. To show the singular impact of these added factors, we specifically exclude spatial structure and iterated interactions. We use a population genetics model where genetic variants within each of two species determine whether the interaction is mutualistic or selfish, the latter being represented by resistance to being exploited or parasitized. We use modelling structures similar to those used in analyses of infectious disease resistance polymorphisms (Antonovics and Thrall 1994; Bowers et al. 1994; Sasaki 2000; Fenton et al. 2009), except that host-parasite or host-pathogen contacts are now represented by pair-wise association of the two interacting species. Because such associations are likely to be dependent on the frequency and density of the interactants, we also include numerical dynamics of the host and parasite. We show that adding these elements of ecological realism facilitates the evolution of mutualism and also allows the possibility of stable genetic polymorphism and mixed strategies that otherwise are not possible with the basic Prisoner's Dilemma assumptions.

Model

We assume there are two species, X and Y, which form pairwise associations that continue till one or both of the interactants die (Fig. 1). This follows the general structure of several previous models of symbioses where individuals of two interacting species are not co-inherited but re-associate each generation (Kostitzin 1935; Law and Dieckmann 1998; van Baalen and Jansen 2001; Genkai-Kato and Yamamura 1999). We exclude the possibility of any population structure or relatedness by assuming that all interactions occur at random, there is no "co-inheritance" of pairs, and that the dynamics are deterministic.

We first describe how reciprocal exploitation can be represented by the Prisoner's Dilemma. This has been pointed out before (Doebeli and Knowlton 1998), but we do this in order to explain the model structure, our notation, and how it can be interpreted as a one-locus two-allele population genetic model. We then describe how we incorporate resistance to parasitism (or resistance to being exploited), and numerical dynamics into the model. Table 1 summarizes the symbols used in the paper.

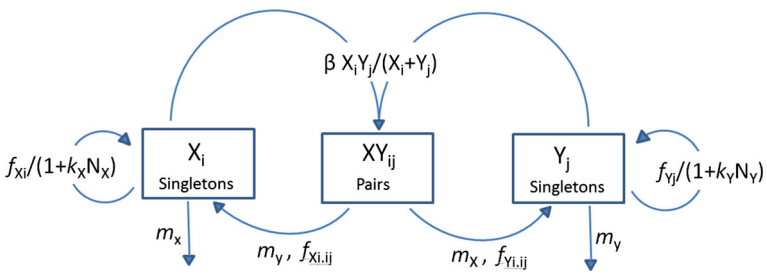

Fig. 1 Overall model structure showing pair formation from singletons, pair disassociation due to mortality, mortality of singletons, and reproduction of singletons and pairs

Table 1 Mathematical symbols used in the text

X, Y	Names for species X and species Y
X_1, X_2	Names of alleles for susceptibility and resistance, respectively, in species X
Y_1, Y_2	Names of alleles for susceptibility and resistance, respectively, in species Y
X_1, X_2	Numbers of singletons of genotypes X_1 and X_2
Y_1, Y_2	Numbers of singletons of genotypes Y_1 and Y_2
XY_{11}, XY_{12}, XY_{21}, XY_{22}	Numbers of genotype X_1 paired with Y_1, numbers of genotype X_1 paired with Y_2, etc
f_x, f_y	Fecundity of susceptible individual of species X or Y
b_x, b_y	Fecundity gain in species X when associated with the susceptible genotype of species Y, and similarly for Y
a_x, a_y	Fecundity loss in susceptible genotype of species X or Y when associated with the other species
c_x, c_y	Cost of resistance of alleles (X_2 or Y_2) expressed as reduction in fecundity
β	Coefficient determining rate of pair formation
P_{11}, P_{12}, P_{21}, P_{22}	Number of newly formed pairs of X_1 with Y_1, X_1 with Y_2, etc
m	Mortality rate, assumed constant for all individuals whether in a pair or not
N_x, N_y	Density of species X or Y
k_x, k_y	Coefficient representing the intensity of density-dependent population regulation
f_{x1}, f_{x2}, f_{y1}, f_{y2}	Fecundity of genotypes X_1, X_2, Y_1, Y_2 as singletons
$f_{x1.11}$, $f_{x1.12}$, $f_{x2.21}$, $f_{x2.22}$	Fecundity of genotype X_1 when in an X_1 Y_1 pair; fecundity of genotype X_1 when in an X_1 Y_2 pair; etc
$f_{y1.11}$, $f_{y1.21}$, $f_{y2.12}$, $f_{y2.22}$	Similar to the previous but for genotypes of Y
ϕ	Frequency of pairs (e.g. number of X in pairs/total number of individuals of X); unsubscripted, as it is only used in contexts where it is the same for both species
Labelling of regions in Figs. 3 and 4: X_P, X_1, X_2	Regions of stable polymorphism, fixation of X_1 and fixation of X_2; and similarly for Y

The subscripts x and y refer to the two species, and the subscripts 1 and 2 refer to susceptible (potentially mutualistic) and resistant (selfish) genotypes, respectively, of either X or Y

Representing reciprocal exploitation

Assume that two species, X and Y, parasitize or exploit each other during their pairwise encounters, but the degree of parasitism varies with genotype (Fig. 2). We assume haploid genetics. When genotypes X_1 and Y_1 associate in pairs, each species gains ($+b_i$; where i = X or Y) more in terms of fitness than the other species loses ($-a_i$; where i = Y or X). When they parasitize each other reciprocally there is more net gain from the association than when they don't parasitize (Fig. 2, top interaction). For example, in arbuscular mycorrhizal relationships, plants normally gain from acquiring phosphorus from fungi, and fungi gain by acquiring carbon in the form of sugars from plants.

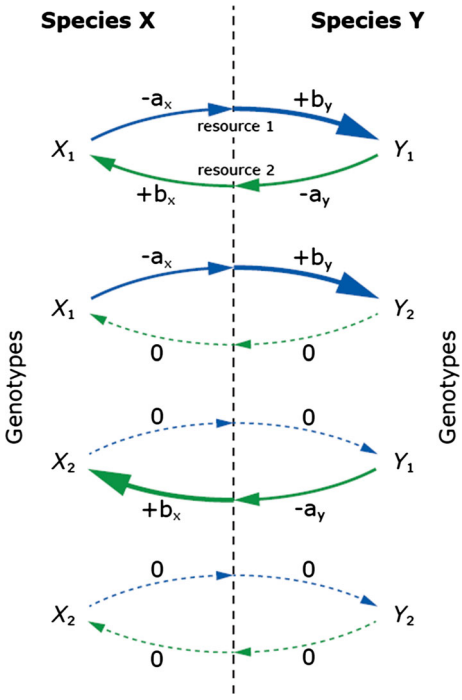

Fig. 2 Illustration of reciprocal parasitism, where values a_i and b_i (i = X or Y) represent fitness losses and gains respectively for two haploid species, X and Y. X_1 and Y_1 represent susceptible genotypes, in that they can be parasitized by the other species, and X_2 and Y_2 represent completely resistant genotypes that cannot be parasitized. The top relationship represents mutualism

Now let there be genetic variation in resistance to being parasitized. We assume for simplicity that resistance is complete such that individuals with alleles for resistance (X_2, Y_2) cannot be parasitized by the other species, but can themselves parasitize their partners if the latter carry an alternative allele for susceptibility (Y_1 and X_1, respectively) (Fig. 2, middle two interactions). If both partners carry resistance alleles (i.e., X_2 and Y_2) they cannot parasitize each other (Fig. 2, bottom interaction). Genetic variation in the strength of mutualistic interactions has been demonstrated in plant-rhizobium systems (Heath and Tiffin 2007; Gorton et al. 2012). Similarly, plant-mycorrhizal relationships are not invariably mutualistic: when arbuscular mycorrhizae infect plants that are normally non-mycorrhizal, they may act as parasites (Veiga et al. 2013); conversely, plants can be parasitic on the fungi (Merckx and Freudenstein 2010).

Such reciprocal parasitism with genetic variation can be translated into a pay-off matrix describing the added benefits and costs to each interactant:

	Y_1	Y_2
X_1	$-a_x + b_x, -a_y + b_y$	$-a_x, +b_y$
X_2	$+b_x, -a_y$	0, 0

If $b > a$, then this matrix translates into the Prisoner's Dilemma, with $+b_i > (-a_i + b_i) > 0 > -a_i$. In these circumstances, it is the selfish strategy (i.e. being resistant) that always wins. In this conceptualization, mutualism (or "co-operation" in Prisoner's

dilemma parlance) evolves when the alleles for susceptibility (Y_1 and X_1) go to fixation in both species. Fixation of an allele for susceptibility in one species and resistance in the other represents a one-sided parasitism (or in Prisoner's Dilemma parlance, the resistant interactant "defects" or is "selfish"). When alleles for resistance go to fixation in both species, their interaction becomes neutral with regard to fitness. Thus the question of how mutualism can evolve from reciprocal parasitism is equivalent to asking how alleles for susceptibility, X_1 and Y_1, can spread in the population in the presence of alleles for resistance, X_2 and Y_2.

Costs of resistance

Resistance costs to parasitism have been shown in plants (Biere and Antonovics 1996; Vila-Aiub et al. 2011), animals (Webster and Woolhouse 1999; Tschirren et al. 2012), and humans (Baker and Antonovics 2012) and are likely to be ubiquitous, as without such costs, all resistances would be expected to go to fixation. To represent a cost of resistance in X_2 and Y_2, we include the parameters c_x, c_y in the pay-off matrix:

	Y_1	Y_2
X_1	$-a_x + b_x, -a_y + b_y$	$-a_x, +b_y - c_y$
X_2	$+b_x - c_x, -a_y$	$-c_x, -c_y$

Note that the costs of resistance are present regardless of whether the individuals are involved in the interactions or not. Under these conditions, the inequality above representing the Prisoner's Dilemma still holds as long as $c < a$ and mutualism cannot evolve.

Pair formation

However, in incipient mutualisms between free living organisms, not every individual associates with every other individual; indeed, where the numbers of two species differ such complete pair formation is impossible. We therefore consider the process of pair formation as a dynamical process. The theory of pair formation in populations is complex, because pair formation occurs by sampling without replacement, and iterative solutions are needed for exact calculations of "pair formation" or "marriage" functions (Gimelfarb 1988). We use a simplified form of the pair formation function of Hadeler (1989):

$$\beta XY/(X + Y) \quad (1)$$

where, β = the rate of pair formation, and X and Y = the numbers of the two species; this function has the property that if beta is less than 1, the number of pairs cannot exceed the smallest number of singletons. Moreover, with this function, the fraction of the total population that is in pairs is independent of the total density. By analogy with epidemiological models (Antonovics et al. 1995), we call this β a coefficient of "frequency-dependent pair formation".

We additionally use the function:

$$\beta XY \quad (2)$$

where, because the frequency of pair formation increases with density of both species, β represents a coefficient of "density-dependent pair formation". To avoid the number of pairs exceeding the number of available singletons, we add the constraint to Eq. 2 that $\beta < 1/(X + Y)$. Again by analogy with disease transmission processes, frequency-dependent pair formation would occur in situations where there is active searching involved in pair formation, whereas density-dependent pair formation would occur where there is mass-action (random) association among individuals.

Reproduction, mortality and density-dependence

For simplicity, we assume that the benefits and costs of the association are expressed purely through differential fecundity. We assume a base fecundity for each genotype, and fecundity gains or losses from the pairwise interactions and from resistance costs are added or subtracted from this base fecundity on a linear scale. This is in keeping with how fitness effects are usually expressed in the canonical Prisoner's Dilemma formulation. Mortality rate, m, is assumed to be the same for all individuals regardless of genotype and whether they are in a pair or not.

Density-dependent regulation acts on fecundity, and takes the form $1/(1 + k_i \times N_i)$, where N_i = density and k_i = the intensity of density-dependence of species X or Y. The two species are assumed to not compete for resources, and can therefore co-exist independently.

Model analysis and simulation

The numerical dynamics were represented by equations of the following form. The full equations (for two genotypes in each species, and for four types of interspecific pairs) are in Supplementary Material 2.

For singletons:

$$dX_1/dt = (f_{x1}X_1 + f_{x1.11}XY_{11} + f_{x1.12}XY_{12})/(1 + k_xN_x) - mX_1 - (P_{11} + P_{12}) + m(XY_{11} + XY_{12}) \quad (3)$$

and similarly for X_2, Y_1, and Y_2.

Here the rate of change in the numbers of singletons of genotype X_1 is determined by the following terms: (1) its fecundity (as a singleton and when in pairs) divided by a density effect, (2) loss due to mortality of singletons, (3) loss of singletons due to pair formation; and (4), gain of singletons due to mortality of the alternate member when in pairs.

For pairs:

$$dXY_{11}/dt = P_{11} - 2m\,XY_{11} \quad (4)$$

and similarly for XY_{12}, XY_{21}, XY_{22}.

Here the rate of change in the numbers of pairs of genotype X_1 and Y_1 is determined by the terms: (1) pair formation from singletons, (2) loss of pairs due to mortality of one or other of the members of the pair. When pair formation is frequency dependent, $P_{ij} = \beta XY/(N_x + N_y)$ and when it is density-dependent, $P_{ij} = \beta XY$ (where now i, j = genotype1 or 2). For singletons: fecundity of $X_1 = f_{x1}$, and fecundity of $X_2 = f_{x2} = f_{x1} - c_x$, and similarly for Y. For pairs: fecundity of X_1 with $Y_1 = f_{x1.11} = f_{x1} - a_x + b_x$, fecundity of X_1 with $Y_2 = f_{x1.12} = f_{x1} - a_x$, etc., and similarly for Y.

Analytical solutions of invasion conditions for mutualism and conditions for genetic polymorphism were only possible for some special cases (see "Results"). Otherwise, the model was implemented (Supplementary Material 1) using 'deSolve' Version 1.10-8 in R (Soetaert et al. 2010), with the function 'ode' (default 'lsoda') using Runge–Kutta asymptotic discretization. Equilibria were determined by running simulations >10,000 generations, and confirmed by testing for return to equilibrium from displaced values; all reported equilibria were stable and independent of starting numbers (e.g. Supplementary Material 4, Fig. S4).

Results

Analytical solutions

Analytical solutions were possible for some special cases where pair formation was frequency-dependent. The derivations are in Supplementary Materials 2 and 3.

If we assume parameter values for species X and Y are identical (and removing subscripts x or y), then mutualism (susceptible genotypes X_1 and Y_1) will invade when rare if $c > a\phi$, where, ϕ = frequency of each species in pairs (Supplementary Material 2). At

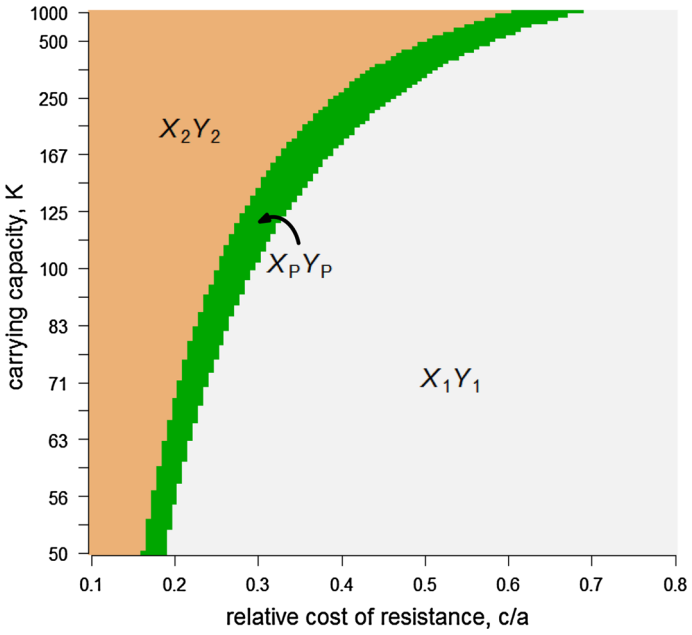

Fig. 3 Phase diagram showing outcomes of simulations for varying values of carrying capacity K (obtained by varying *k*) and varying values of the relative cost of resistance (*c*/*a*) for the symmetrical case when values for X and Y are the same. *Note*: Equilibrium carrying capacities depend on the nature of the pairwise interactions. Other parameters: $f_x, f_y = 1$; $m_x, m_y = 0.5$; $a_x, a_y = 0.2$; $b_x, b_y = 0.5$; $\beta = 0.005$ for density-dependent pair formation. Region X_2Y_2 represents spread of selfish (resistant) genotypes, and region X_1Y_1 represents spread of mutualistic (susceptible) genotypes, respectively. Region X_PY_P represents polymorphism in both species

equilibrium, we show that $\phi = \beta/(4\ m + \beta)$, and therefore mutualism spreads if $c > a\beta/(4\ m + \beta)$.

We obtain the conditions for polymorphism as follows (Supplementary Material 3). If we assume one species, say Y, is fixed for susceptibility (Y_1) then mutualism (i.e. susceptible genotype X_1) will invade when rare if

$$f - a + b > (f - c)(1 - \phi) + (f + b - c)\phi$$

Similarly, resistance (X_2) will invade when rare if

$$f - c + b > f(1 - \phi) + (f - a + b)\phi$$

This leads to the conclusion that there exists a region of stable polymorphism of X_1 and X_2 defined by the inequalities:

$$(1 - \phi) + c_x/b_x > a_x/b_x > (c_x/b_x - (1 - \phi))/\phi$$

Simulations

Mutualism evolves (i.e. both species become susceptible) at values of c considerably less than a (Fig. 3), i.e. when it would not do so under the basic Prisoner's Dilemma model, agreeing with the analytical result above. When pair formation is frequency-dependent (Eq. 1), symmetrically varying density-dependent population regulation ($k_x = k_y$) has no effect because the fraction of individuals in pairs vs. singletons remains unchanged. When pair formation is density dependent (Eq. 2), however, the evolution of mutualism depends on carrying capacity (Fig. 3); at higher carrying capacities mutualism only evolves when costs of resistance are higher. There is additionally a small region at the boundary of the phase plane between fixation of X_2Y_2 (=selfish in X and Y) and fixation of X_1Y_1 (=mutualism in X and Y) where both species are stably polymorphic (labelled "X_PY_P" in Fig. 3).

When the parameters in the two interacting species are unequal, a range of further outcomes is possible. For example, Fig. 4 shows the outcomes when carrying capacities are varied and pair formation is density-dependent. (The outcomes for frequency-dependent pair formation are shown in Supplementary Material 4, Fig. S1). When costs are low, resistance evolves in both species (X_2, Y_2 fixed) and when costs are high mutualism evolves in both (X_1, Y_1 fixed). When species X has a higher carrying capacity than Y (Fig. 4, bottom rows; the converse holds when Y is more abundant, Fig. 4, top rows), there is a region "X_PY_2" at intermediate costs where the more abundant species is polymorphic (both alleles X_1 and X_2 are present at equilibrium) while the least abundant species is resistant (Y_2). Here Y, the rarer species, is now effectively a parasite while X is a host polymorphic for resistance; the rarer species is in relatively more pairs, and therefore bears a lower net cost of resistance. At somewhat higher costs there is region "X_1Y_2" where X is fixed for X_1 (and acts as a susceptible host), while Y is fixed for Y_2 (and acts as a selfish, i.e. resistant, parasite). At even higher costs, region "X_1Y_P" represents the situation where the more abundant species X remains monomorphic for mutualism (X_1), but the less abundant species Y is now polymorphic for mutualism versus selfishness (Y_1, Y_2). There is always a small region "X_PY_P" where there is polymorphism in both species. Unequal costs also generate these types of species interactions (Supplementary Material 4. Figs. S2-4), as does variation in other parameters such as β (Fig. S5).

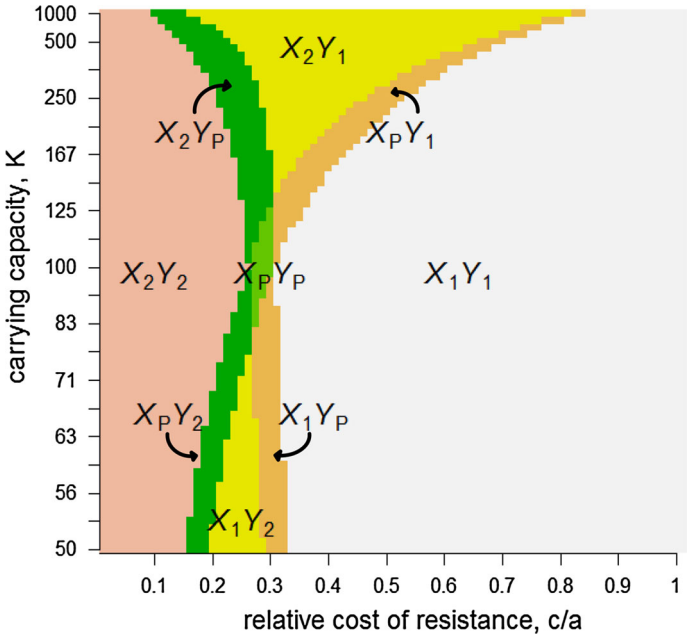

Fig. 4 Phase diagram showing regions of equilibria for a range of relative costs of resistance, *c/a*, and a range of unequal carrying capacities. Carrying capacity of X_1 as singletons = 100 ($k_x = 0.01$), while carrying capacity of Y_1 as singletons varies from 50 to 1000 (k_y varies from 0.02 to 0.001). *Vertical axis* shows carrying capacities of Y1. *Note*: these are not equilibrium carrying capacities, as these depend on the nature of the pairwise interactions. Other parameters: $f_x, f_y = 1$; $m_x, m_y = 0.5$; $a_x, a_y = 0.2$; $b_x, b_y = 0.5$; $\beta = 0.005$ for density-dependent pair formation

Discussion

The problem of the evolution of mutualism from reciprocal parasitism has previously been restated in terms of the Prisoner's Dilemma (Doebeli and Knowlton 1998), but here we additionally place the Dilemma in a context (a) where the frequency of interaction is influenced by the density of the interactants, (b) where there is density-dependent population regulation of the interactants, and (c) where "selfishness" or "defection", instantiated as resistance to parasitism, is costly both in the presence and absence of the interaction. The most striking result of this analysis is that with these additions to the basic Prisoner's Dilemma model, the conditions for the evolution of mutualism are generally more favourable than envisaged by the simple pay-off matrix.

Moreover, we show that the evolutionary outcomes are very dependent on rates of pair formation and therefore on fecundity, mortality, and strength of density dependence, all of which will determine the population sizes of the interactants. These in turn are likely to be highly dependent on resources, abiotic factors, and community interactions, i.e. the "ecological context". Our results emphasize that with such added ecological realism, multiple evolutionary directions are possible that depend on parameter values (see Fig. 4). In real-world ecological contexts, the parameter values themselves would be under selection and also dependent on the environmental conditions, implying a likely "fluidity"

in the evolutionary directions that ensue from interactions among incipient mutualists (rather than direct selection "for" such mutualisms, followed by selection "for" adaptations to maintaining them). Phylogenetic studies have confirmed that many mutualisms are evolutionarily very labile (Sachs and Simms 2008) especially when there is no co-transmission of the interactants (ectomycorrhizal and other fungi: Tedersoo et al. 2010; Egger 2006; Chaverri and Samuels 2013; ants and acacias: Heil et al. 2009; orchids and fungi: Veldre et al. 2013; and bacteria and a wide range of other organisms: Sachs et al. 2011).

Our results also support the idea that organisms may evolve facultative strategies with responses to an association dependent on resource availability or levels of association (Bronstein 1994). The importance (not to mention, difficulty) of distinguishing "mixed evolutionarily stable strategies" (i.e. genetic polymorphisms) from "conditional strategies" (i.e. environmentally induced or behavioural variants) has long been emphasized in game theory (Maynard Smith 1979).

The basic pay-off matrix makes the assumption that all individuals are interacting pairwise with a member of the other species (everyone plays the 'game'), whereas this is not only unlikely, but often impossible given unequal population numbers of the interacting species. It may be thought that if not every individual in a population is in an interaction, then the evolutionary pressures would simply be less but the outcome the same, but we show that the outcome can be qualitatively different.

Under many parameter combinations a stable genetic polymorphism (i.e. a mixture of "defection" and "co-operation" strategies) is possible, an outcome not possible with the basic pay-off matrix of the Prisoner's Dilemma. Indeed this study was in part stimulated by previous work showing that adding numerical dynamics to purely genetic models greatly influences co-evolutionary outcomes. Specifically, polymorphisms in resistance in some host-parasite systems (Antonovics and Thrall 1994; Bowers et al. 1994; Boots et al. 2014) are only possible when numerical dynamics are included. Analogous polymorphisms (regions "$X_P Y_2$", and "$X_2 Y_P$" in the phase diagrams) also emerge in the present study. Whether and under what conditions such polymorphisms would be maintained over the longer term in the face of small mutational changes or modifier genes deserves further investigation. In the case of host-parasite systems, whether the polymorphism is maintained or eliminated by ensuing small mutations depends on the shape of the curve relating cost of resistance to the ensuing benefit of increased resistance (Boots and Haraguchi 1999; Baker and Antonovics 2012). Changing the genetic assumptions about the evolutionary process could also alter the outcome: Scheuring (2005) has argued that the mechanism of tit-for-tat will not lead to the evolution of mutualisms within an adaptive dynamics framework that assumes small incremental mutations.

We have made the assumption that the costs of resistance are present even in the absence of the interaction, and this is regardless of whether the resistance is constitutive or inducible. If the 'resistant' genotypes X_2 and Y_2 only suffer a cost of mounting resistance during the pair formation itself (i.e. there are additional costs of induced resistance during the interaction) then in the pay-off matrix, this cost would act additively with respect to a and can therefore be subsumed in a new parameter, say a', such that mutualism would still only evolve if $c > a'$; it would not change our basic conclusions. However, in many, if not all, host-parasite interactions, costs of resistance are present even in the absence of a pathogen (Biere and Antonovics 1996; Vila-Aiub et al. 2011; Webster and Woolhouse 1999; Tschirren et al. 2012; Baker and Antonovics 2012) and are likely to be quite general, as without such costs organisms would just accumulate ever increasing resistances. In other studies, costs have been posited by the inclusion of "punishment" in models of the

evolution of mutualism (Boyd and Richerson 1992; Dreber et al. 2008), and these are imposed differentially during the interaction itself.

While we have deliberately excluded the usual factors that resolve the Prisoner's Dilemma, this exclusion has been for heuristic and not biological reasons. Therefore we certainly do not claim that all mutualisms evolve from reciprocal parasitism. There are likely many pathways to mutualism; for example, mutualisms may evolve from "one-sided" parasitism (Genkai-Kato and Yamamura 1999; Wang and Wu 2014), or as a consequence of "by-product benefits" (Connor 1995; Hom and Murray 2014) where individuals may further evolve to "trade" excess resources in an optimal manner (Noë et al. 2001; De Mazancourt and Schwartz 2010). It would also be of interest to examine the processes described here in a spatial context; for example, including limited dispersal even where there is no actual co-transmission could facilitate the evolution of mutualism (Ronsheim 1997; Wilkinson 1997).

Our model is simple in that it only includes complete rather than partial resistance, the host-parasite interaction genetics is haploid, and it does not incorporate the more complex genetics of many host-pathogen interactions (e.g. gene-for-gene). Nor have we presented the outcomes of all possible parameter combinations, as it seems rather superfluous to do so in the absence of an appropriate empirical system where the posited processes might be occurring. For example, we have not especially focused on the mortality rate m, but our analysis shows that when m is high, there is likely to be a high frequency of singletons, with the result that resistance is 'effectively' much more costly in short lived individuals because more individuals of a resistant genotype will not be playing the 'game'.

This study implicitly emphasises that the evolution of mutualism presents a formidable research challenge. First, the relevant fitness gains and losses cannot be simply estimated by the marginal fitness of the partners in the associations; there are only four marginal fitnesses in the "pay-off" matrix, but complete specification requires that estimates are also needed of the fitness costs of different physiological or biochemical pathways whereby reciprocal consumer-resource dynamics are instantiated (see Fig. 2). Second, in the incipient phases of a mutualism, the interactions are likely to be partial (with few overt and certainly no spectacular 'adaptations'), so the focus of any research would be on genetic variation within species rather than fixed species differences; co-inheritance or spatial structure are likely to be additional factors. An increasing number of studies are showing that there are strong genotype x genotype interactions among pairs of mutualists, suggesting partner specificity in such interactions (Heath and Tiffin 2007); and genomic studies to identify the loci involved are likely to lead to a better understanding of the costs and benefits of different components of these interactions (Gorton et al. 2012). Third, the processes modelled and discussed here are likely to be occurring in the "rich stew" of microbial interactions, or with plant- or animal-microbe interactions, and therefore till recently they have been technically difficult to characterize either genetically or phenotypically (Aguilar-Trigueros et al. 2014).

However, this situation is changing rapidly, and experimental systems that generate cross-feeding between micro-organisms promise to provide a tractable route for investigating the evolutionary processes discussed here (Tanouchi et al. 2012; Tan et al. 2015). Indeed a recent study by (Pande et al. 2014) using a series of strains engineered to have deletion and over-production mutations for different amino acids showed that cross feeding mutants could not only coexist stably with each other, but could also be invaded by auxotrophs not providing the fitness benefit of over-production, and stably coexist with them. While their measured costs and benefit parameters are not placed into a theoretical context, it is very conceivable that this experimental approach could be used to test the

postulates presented in this paper by measuring the appropriate parameters, and varying the density and frequency of the interactions. Therefore, we hope the ideas presented here will further stimulate the investigation of evolutionary processes at the parasitic-mutualism continuum in both natural and experimental systems.

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