Understanding the role of eco-evolutionary feedbacks in host-parasite coevolution

Ben Ashby[a,b,*], Ryosuke Iritani[b,c,†], Alex Best[d,‡], Andy White[e,§], and Mike Boots[b,c,¶]

a. Department of Mathematical Sciences, University of Bath, Bath, BA2 7AY, UK
b. Integrative Biology, University of California Berkeley, Berkeley, CA, USA
c. Biosciences, College of Life and Environmental Sciences, University of Exeter, Cornwall Campus, Penryn, Cornwall, TR10 9EZ, UK
d. School of Mathematics and Statistics, University of Sheffield, Sheffield, S3 7RH, UK
e. Department of Mathematics and the Maxwell Institute for Mathematical Sciences, Heriot-Watt University, Edinburgh, EH14 4AS, Scotland, UK

* Corresponding author: benashbyevo@gmail.com

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ABSTRACT

It is widely recognised that eco-evolutionary feedbacks can have important implications for evolution. However, many models of host-parasite coevolution omit eco-evolutionary feedbacks for the sake of simplicity, typically by assuming the population sizes of both species are constant. It is often difficult to determine whether the results of these models are qualitatively robust if eco-evolutionary feedbacks are included. Here, by allowing interspecific encounter probabilities to depend on population densities without otherwise varying the structure of the models, we provide a simple method that can test whether eco-evolutionary feedbacks per se affect evolutionary outcomes. Applying this approach to explicit genetic and quantitative trait models from the literature, our framework shows that qualitative changes to the outcome can be directly attributable to eco-evolutionary feedbacks. For example, shifting the dynamics between stable monomorphism or polymorphism and cycling, as well as changing the nature of the cycles. Our approach, which can be readily applied to many different models of host-parasite coevolution, offers a straightforward method for testing whether eco-evolutionary feedbacks qualitatively change coevolutionary outcomes.

INTRODUCTION

There is a clear interdependence between ecological and evolutionary dynamics. A classic example is the spread of a rare allele conferring resistance to an infectious disease: the strength of selection depends both on the prevalence of disease and on intrinsic costs associated with resistance (Haldane 1949; Antonovics & Thrall 1994; Bowers *et al.* 1994; Boots & Haraguchi 1999). As the allele increases in frequency the prevalence of disease falls, thus reducing selection for resistance. Hence, the ecological or population dynamics are intrinsically linked to the evolutionary dynamics, forming an "eco-evolutionary feedback" (Post & Palkovacs 2009) (sometimes simply referred to as an "ecological" (Boots *et al.* 2009) or "environmental" feedback; (Lion 2018)). These feedbacks are the norm rather than the exception and have been central to explaining the dynamics of laboratory systems (e.g. bacteria-phage, Hesse & Buckling 2016; algae-virus, Frickel *et al.* 2016) and wild populations (e.g. rabbits and myxomatosis, Dwyer *et al.* 1990). Eco-evolutionary feedbacks have long been recognised as important factors in both ecology and evolutionary biology (Haldane 1949; Pimentel 1968; Charlesworth 1971; Roughgarden 1971; Clarke 1972; Slatkin 1979; Taper & Case 1985; Abrams *et al.* 1993; Papkou *et al.* 2016; Lion 2018), leading to the development of a variety of methods for studying eco-evolutionary dynamics (Dieckmann & Law 1996; Geritz *et al.* 1998; Day & Proulx 2004; Day & Gandon 2007; Gandon & Day 2009; Sasaki & Dieckmann 2011; Lion 2018).

Eco-evolutionary methods have been successfully applied to the study of host-parasite coevolution. Yet many studies instead focus only on the evolutionary dynamics, typically by assuming that the population sizes – and hence, the interspecific encounter rates (provided these do not evolve) – for both species are fixed (Table 1). Indeed, our analysis of the literature published between 2000 and 2017 reveals that over half (~54%) of studies with theoretical models of host-parasite coevolution assume constant population sizes (and hence lack eco-evolutionary feedbacks) for one (~2%) or both (~52%) species (Fig. S1 & Table S1; see *Supplementary Material* for details). The lack of eco-evolutionary feedbacks is often not biologically justified, and as such we do not know whether a large and growing number of predictions are robust to this crucial assumption. Moreover, by omitting population dynamics, the effects of genetic bottlenecks, drift, and extinctions may be neglected (Hesse & Buckling 2016). A better understanding of the impact of eco-evolutionary feedbacks on host-parasite coevolution could have important implications for disease management (Grenfell *et al.* 2004), pest control (Payne 1988), and conservation (Mooney & Cleland 2001), as well as for our understanding of core biological phenomena such as sex (Maynard Smith 1978), mate choice (Ashby & Boots 2015), and patterns of diversity across space and time (Clarke 1979; Boots *et al.* 2014).

Reference(s)	Focal point(s)	Infection genetics	Eco-evo. feedbacks
Poullain & Nuismer 2012	host shifts	single-locus	yes
Agrawal & Otto 2006	RQH*	single-locus	no
Gandon & Nuismer 2009	local adaptation	single-/multi-locus	no
Tellier & Brown 2007a, b	polymorphism	single-/multi-locus	no
Segarra 2005	polymorphism	single-/multi-locus	no
Agrawal & Lively 2002	cycling	multi-locus	no
Ashby & Boots 2017	cycling	multi-locus	yes
Sasaki 2000	cycling, polymorphism	multi-locus	no
Song *et al.* 2015	cycling, population dynamics	multi-locus	yes
MacPherson & Otto 2018	cycling, population dynamics	multi-locus	yes
Gokhale *et al.* 2013	cycling, population dynamics	multi-locus	yes
Engelstädter 2015	cycling, RQH*	multi-locus	no
Kouyos *et al.* 2007, 2009	cycling, RQH*	multi-locus	no
Ashby & Gupta 2014	cycling, RQH*	multi-locus	yes
Fenton *et al.* 2009, 2012	dynamics	multi-locus	no
Fenton & Brockhurst 2007	epistasis, dynamics	multi-locus	no
Ashby *et al.* 2014a, b	resistance, infectivity	multi-locus	yes
Otto & Nuismer 2004	RQH*	multi-locus	no
Peters & Lively 2007	RQH*	multi-locus	no
Salathé *et al.* 2008, 2009	RQH*	multi-locus	no
Ashby & King 2015	RQH*	multi-locus	yes
Lively 2010b	RQH*	multi-locus	yes
Weitz *et al.* 2005	bacteria-phage, polymorphism	quantitative	yes
Best *et al.* 2017	cycling, specificity	quantitative	yes
Boots *et al.* 2014	diversity, specificity	quantitative	yes
Nuismer *et al.* 2005	dynamics, cycling, variance	quantitative	no
Nuismer *et al.* 2007	dynamics, cycling	quantitative	no
Ashby & Boots 2015	mating, sexual transmission, virulence	quantitative	yes
Best *et al.* 2010b	resistance, infectivity	quantitative	yes
Restif *et al.* 2003	resistance, virulence	quantitative	yes
Bonds *et al.* 2005	sociality, virulence	quantitative	yes
Kada & Lion 2015	superinfection, virulence, recovery	quantitative	yes
Best *et al.* 2010a, 2014	tolerance, sterility	quantitative	yes
Gandon *et al.* 2002	virulence, reproduction	quantitative	yes

Table 1 – Examples of host-parasite coevolution models from the literature analysis of studies published between 2000 and 2017 (see *Supplementary Material*), illustrating the various modelling assumptions and focal points. Key: *RQH: Red Queen Hypothesis for the evolutionary maintenance of sex.

A key reason eco-evolutionary feedbacks may play an important role in host-parasite coevolution is because they result in direct frequency-dependent selection (direct FDS), so that selection depends not only on the distribution of traits in the non-focal population (indirect FDS), but also on the distribution of traits in the focal population (Geritz *et al.* 1998; Tellier & Brown 2007a, b). Direct FDS is a crucial factor in the Adaptive Dynamics literature, as it is a prerequisite for evolutionary branching (and hence stable trait polymorphism) to occur (Geritz *et al.* 1998). Yet its importance is often overlooked in models of host-parasite coevolution that lack population dynamics. As an exception, Tellier & Brown (2007a, b) showed that direct FDS is necessary to generate stable trait polymorphism in a gene-for-gene model even when population sizes are constant between host generations. The authors achieved this by assuming multiple parasite generations occur per host generation and that parasite fitness within each host generation depends on the current distribution of parasites, thereby creating direct FDS. Since host availability declines across successive parasite generations within each host generation, this is effectively a temporary eco-evolutionary feedback on the parasite.

When eco-evolutionary feedbacks are omitted from models of host-parasite coevolution it is usually for simplicity and to provide greater analytic tractability, especially when there are major gene interactions (Table 1). While some studies have been able to gain analytic insights into eco-evolutionary models with population genetics or using the Price equation (Day & Gandon 2007; Gandon & Day 2009), most use numerical approaches as opportunities for analytic insights tend to be limited (May & Anderson 1983; Frank 1991; Lively 2010b; Gokhale *et al.* 2013; Ashby *et al.* 2014a; Ashby & King 2015; Song *et al.* 2015; Ashby & Boots 2017; MacPherson & Otto 2018). Many studies make the alternative assumption that traits are quantitative (many loci with small additive effects) (Table 1), using techniques such as Adaptive Dynamics to gain analytic insights (Dieckmann & Law 1996; Geritz *et al.* 1998). Some of the broader differences in results between these two classes of models may therefore be due to contrasting assumptions about the genetics or analytical method rather than the presence or absence of eco-evolutionary feedbacks.

The crucial question, however, is does the assumption of fixed population sizes in purely evolutionary models qualitatively impact on the outcome of coevolution? One approach to answering this question is to compare the results from a purely evolutionary model to those from a full eco-evolutionary model (Ashby & Boots 2017; MacPherson & Otto 2018). While this provides insights as to whether results are consistent in more realistic settings with eco-evolutionary feedbacks, fundamental differences between the two approaches prevent simple comparisons. This is because purely evolutionary and eco-evolutionary models typically differ in structure and parameterisation, with contrasting methods for defining fitness. It is therefore very difficult to unequivocally attribute any changes in the results to the feedbacks themselves. For example, Nuismer *et al.* (2007) and Best *et al.* (2010b) both

analyse the same quantitative trait where hosts and parasites vary in their degree of specialism and generalism, but the former used a non-ecological approach with fitness defined arbitrarily, while the latter derived fitness from an explicit birth-death process. One cannot interpret the precise effects of eco-evolutionary feedbacks by comparing these purely evolutionary and eco-evolutionary models, as the differences may be caused by other factors. An alternative numerical approach is to artificially remove population dynamics from an eco-evolutionary model by continually resetting the population sizes to a particular level, thereby preventing eco-evolutionary feedbacks (Gokhale *et al.* 2013; Song *et al.* 2015). The advantage of this approach is that it does not require a change in model structure or parameterisation, and therefore any differences can be directly attributed to eco-evolutionary feedbacks. However, this method only allows one to test the effects of removing eco-evolutionary feedbacks from a model, and cannot be used to introduce eco-evolutionary feedbacks into models that initially lack them.

Here we propose a novel method for understanding the impact of eco-evolutionary feedbacks in host-parasite coevolution. By introducing eco-evolutionary feedbacks into purely evolutionary models, we are able to assess whether eco-evolutionary feedbacks *per se* impact the results. Crucially, unlike comparisons between purely evolutionary and eco-evolutionary models, our approach does not require a change in the structure or parameterisation of the model, nor in the method of analysis. Hence any changes in the results are directly attributable to eco-evolutionary feedbacks. We demonstrate the utility of our method by applying it to a variety of models from the literature, showing that including eco-evolutionary feedbacks often leads to a fundamental change in the results. Specifically, we examine the effect of eco-evolutionary feedbacks on: (i) the stability of cycles in a single-locus model; (ii) polymorphism, and the stability and nature of fluctuating dynamics in a multi-locus model; and (iii) evolutionary branching in a quantitative trait model.

MODEL DESCRIPTION

We consider the impact of eco-evolutionary feedbacks on a simple model of host-parasite coevolution with n_H host types and n_P parasite types. Each host and parasite type may correspond to either a continuous (quantitative) trait value or a particular genotype with a small number of loci. The former assumes small additive effects between many loci, whereas the latter assumes potentially epistatic effects among a few major loci. For simplicity, we assume that hosts and parasites are haploid and asexual.

Let x_i be the defensive trait of host type $i \in \{1, \dots, n_H\}$, which is at density H_i and frequency h_i. Similarly, let y_j be the offensive trait of parasite type $j \in \{1, \dots, n_P\}$, which is at density P_j and frequency p_j. The total population densities are therefore $H = \sum_{i=1}^{n_H} H_i$ and $P =$

$\sum_{j=1}^{n_P} P_j$. We define the fitness (per-capita growth rates) of each host and parasite type to be $m_i^H(P, H, p_1, \dots, p_{n_P})$ and $m_j^P(H, P, h_1, \dots, h_{n_H})$, respectively. These functions capture the effects of interspecific interactions, costs associated with defensive/offensive traits, and any other factors on growth. For simplicity, we assume that fitness does not directly depend on the frequencies of conspecifics, in line with most models of host-parasite coevolution (note, however, that in real populations the frequency distribution of conspecifics are likely to have effects on fitness which are not captured by these models). The population dynamics for each type are given by:

$$\frac{dH_i}{dt} = m_i^H(P, H, p_1, \dots, p_{n_P})H_i \quad (1a)$$

$$\frac{dP_j}{dt} = m_j^P(H, P, h_1, \dots, h_{n_H})P_j \quad (1b)$$

Summing over the above equations yields the dynamics at the population level:

$$\frac{dH}{dt} = \bar{m}_H(P, H, p_1, \dots, p_{n_P})H \quad (2a)$$

$$\frac{dP}{dt} = \bar{m}_P(H, P, h_1, \dots, h_{n_H})P \quad (2b)$$

where $\bar{m}_H(P, H, p_1, \dots, p_{n_P}) = \sum_{i=1}^{n_H} h_i m_i^H(P, H, p_1, \dots, p_{n_P})$ and $\bar{m}_P(H, P, h_1, \dots, h_{n_H}) = \sum_{j=1}^{n_P} p_j m_j^P(H, P, h_1, \dots, h_{n_H})$ are mean population fitnesses (per-capita growth rates).

Since the frequencies of the types are $h_i = \frac{H_i}{H}$ and $p_j = \frac{P_j}{P}$, it can be shown using the quotient rule that the frequency dynamics are given by:

$$\frac{dh_i}{dt} = h_i\left(m_i^H(P, H, p_1, \dots, p_{n_P}) - \bar{m}_H(P, H, p_1, \dots, p_{n_P})\right) \quad (3a)$$

$$\frac{dp_j}{dt} = p_j\left(m_j^P(H, P, h_1, \dots, h_{n_H}) - \bar{m}_P(H, P, h_1, \dots, h_{n_H})\right) \quad (3b)$$

These are the well-known replicator equations (Schuster & Sigmund 1983), which are commonly used to model host-parasite coevolution. However, while it is clear that replicator dynamics (equation 3) can be derived from (and hence naturally coupled with) population dynamics (equations 1-2), many models ignore population dynamics and instead focus only on the evolutionary dynamics given by the replicator equations (Table 1). This is typically achieved by assuming that population sizes are fixed (equivalently, mean population fitness – as defined above – is zero), in which case there are no population

dynamics to consider and one can therefore focus solely on the evolutionary dynamics in equation (3). This, of course, assumes that evolutionary changes have no impact on population sizes, and as a result, contact rates between hosts and parasites remain constant. Hence, an increase in host resistance, for example, has no impact on the density of parasites or the force of infection, in contrast to standard epidemiological and eco-evolutionary modelling. Under these assumptions, one can ignore the population (density) dynamics given by equations (1)-(2) and focus solely on the evolutionary (frequency) dynamics in equation (3), with fitnesses now given by $m_i^H(p_1, \dots, p_{n_P})$ and $m_j^P(h_1, \dots, h_{n_H})$. As such, these models lack potentially important eco-evolutionary feedbacks whereby population dynamics both affect and are affected by evolutionary dynamics.

We propose reintroducing and examining the impact of eco-evolutionary feedbacks in this class of models by relaxing the restrictive assumption of fixed population sizes, and using equations (1)-(3) to recouple the population and evolutionary dynamics. Such an approach would make it possible to test whether the results from models without eco-evolutionary feedbacks are robust when these effects are included. It would also be useful to test to what extent the results are robust to the lack of eco-evolutionary feedbacks. For example, do the results hold if there is only weak coupling between population and evolutionary dynamics (e.g. if changes in population sizes have little impact on selection)? In other words, how does the strength of eco-evolutionary feedbacks impact on the results?

We introduce variable eco-evolutionary feedbacks into non-eco-evolutionary models by: (1) independently manipulating the degree to which changes in abundance affect the probability of that a host encounters a parasite, $z_H(P)$, and vice versa, $z_P(H)$; and (2) potentially allowing population regulation by other factors (e.g. competition for resources, other species interactions), controlled by functions $q_H(H)$ and $q_P(P)$. For instance, if the density of the host population is high and the density of parasites is low, then an average host may be unlikely to encounter a parasite due to their relative scarcity $(z_H(P) \ll 1)$, whereas an average parasite may be likely to encounter a potential host due to their relative abundance $(z_P(H) \approx 1)$. In models that lack eco-evolutionary feedbacks, the host-parasite encounter rates are effectively constant regardless of population or evolutionary dynamics (i.e. $z_H(P)$ and $z_P(H)$ are fixed). If the population dynamics of both species are entirely regulated by the host-parasite interaction, then $q_H(H)$ and $q_P(P)$ are constant. We allow for the possibility of population regulation by factors outside the host-parasite relationship to capture a wide range of scenarios. For example, the population densities could also be regulated by resource availability (e.g. nutrients or intermediate hosts), predation, and other parasites.

The eco-evolutionary dynamics are now given by:

$$\frac{dH}{dt} = \bar{m}_H\left(z_H(P), q_H(H), p_1, \dots, p_{n_P}\right)H \tag{4a}$$

$$\frac{dP}{dt} = \bar{m}_P\left(z_P(H), q_P(P), h_1, \dots, h_{n_H}\right)P \tag{4b}$$

$$\frac{dh_i}{dt} = h_i\left(m_i^H\left(z_H(P), q_H(H), p_1, \dots, p_{n_P}\right) - \bar{m}_H\left(z_H(P), q_H(H), p_1, \dots, p_{n_P}\right)\right) \tag{4c}$$

$$\frac{dp_j}{dt} = p_j\left(m_j^P\left(z_P(H), q_P(P), h_1, \dots, h_{n_H}\right) - \bar{m}_P\left(z_P(H), q_P(P), h_1, \dots, h_{n_H}\right)\right) \tag{4d}$$

In principle, the functions $q_H(H)$, $q_P(P)$, $z_H(P)$ and $z_P(H)$ can take a variety of forms and will clearly depend on the underlying biology of the system in question. For simplicity, in the examples that follow we assume that factors outside the host-parasite relationship have additive effects (i.e. the population growth rates can be decomposed into $m_i^H\left(z_H(P), q_H(H), p_1, \dots, p_{n_P}\right) = \tilde{m}_i^H\left(z_H(P), p_1, \dots, p_{n_P}\right) - q_H(H)$ and $m_j^P\left(z_P(H), q_P(P), h_1, \dots, h_{n_H}\right) = \tilde{m}_j^P\left(z_P(H), h_1, \dots, h_{n_H}\right) - q_P(P)$). This means that the replicator equations (4c-d) remain independent of $q_H(H)$ and $q_P(P)$, and hence any population regulation effects outside the host-parasite interaction only impact on the evolutionary dynamics through the encounter probability functions $z_H(P)$ and $z_P(H)$. We assume that the encounter probabilities for each species vary linearly with total population density (the results are similar for non-linear relationships, as shown in the *Supplementary Material*), with:

$$z_H(P) = \begin{cases} \dfrac{a_P P}{P_{max}} + (1 - a_P) & if\ P > 0 \\ 0 & if\ P = 0 \end{cases} \tag{5a}$$

$$z_P(H) = \begin{cases} \dfrac{a_H H}{H_{max}} + (1 - a_H) & if\ H > 0 \\ 0 & if\ H = 0 \end{cases} \tag{5b}$$

where H_{max} and P_{max} are the maximum densities allowed for each population and $a_H, a_P \in [0,1]$ control the strength of the eco-evolutionary feedbacks in each population. The 'strength of the eco-evolutionary feedbacks' can also be thought of as the 'degree to which the encounter probabilities depend on population densities'. When $a_H, a_P = 0$ the encounter probabilities are always equal to 1 and so the evolutionary dynamics do not depend on the population dynamics. Note that since $q_H(H)$ and $q_P(P)$ only impact the replicator equations indirectly through their effects on $z_H(P)$ and $z_P(H)$, these terms have no impact on the evolutionary dynamics when $a_H, a_P = 0$. Conversely, when $a_H, a_P = 1$ the encounter probabilities are equal to the relative densities of each population, which means we have mass-action kinetics (e.g. halving the density of parasites halves the probability of encountering a parasite). These two scenarios lie at the extremes of a spectrum of possible relationships between population density and encounter probabilities. In principle, changes

in population size may result in behavioural or environmental changes that impact on encounter probabilities, such as effects on foraging, mating, inter/intraspecific competition, social structure, and dispersal. For example, dispersal in European badgers (*Meles meles*) increases at low population densities, which influences disease spread and limits the efficacy of culling as a control measure for bovine tuberculosis (Rogers *et al.* 1998; Bielby *et al.* 2014). We therefore allow the extent to which encounter probabilities depend upon population densities to vary, so that our framework can be applied to a wide range of biological scenarios. For small positive values of a_H and a_P the encounter probabilities, and in turn, the evolutionary dynamics, depend only weakly on population sizes, hence we say that the eco-evolutionary feedbacks are relatively 'weak'. For instance, if dispersal increases dramatically at lower densities then reductions in encounter probabilities due to there being fewer individuals in the population may be largely offset by increased movement among the remaining individuals. For larger values of a_H and a_P, the encounter probabilities depend predominantly on population densities and therefore the population and evolutionary dynamics are more closely linked, so we say that the eco-evolutionary feedbacks are relatively 'strong'. For example, if dispersal only increases slightly at lower densities then the overall encounter probabilities will depend much more closely on population sizes. Note that for $0 < a_H, a_P < 1$ there is a discontinuity at $H, P = 0$, since one cannot have a positive encounter probability if there are no individuals in the population. However, when either population is driven extinct coevolution can no longer occur and so the models terminate at this point.

The parameters a_H and a_P allow us to independently manipulate the strength of the eco-evolutionary feedback on each population. In practise, this means we are able to start from models with no population dynamics effects on evolutionary dynamics $(a_H, a_P = 0)$ and vary the strength of the eco-evolutionary feedbacks to determine to what extent the results are robust. In other words, are the results consistent if the encounter rates are roughly constant, or are even weak feedbacks sufficient to fundamentally change the outcome? Note that these functions (and those in the *Supplementary Material*) are mathematically convenient ways to vary the strength of the eco-evolutionary feedbacks between the two extremes at $\alpha_H, \alpha_P = 0$ and $\alpha_H, \alpha_P = 1$ and are not intended to capture any particular host-parasite interaction; they are merely an approximation to the more complex dynamics of real systems (i.e. if parasite density increases, the probability of encountering a parasite increases). As such, one should interpret variation in intermediate values of α_H and α_P in broad terms (e.g. by comparing small vs large α_H, α_P to contrast weak and strong feedbacks) rather than focus on specific values of α_H, α_P between 0 and 1. This is because the purpose of our method is to test the robustness of the results from a class of purely evolutionary models to the assumption of no eco-evolutionary feedbacks, rather than to reproduce the dynamics from any particular eco-evolutionary model or biological scenario. Thus the primary question of interest is: to what extent does assuming constant encounter probabilities affect the results?

EXAMPLES

We demonstrate how the framework in equations (4-5) can be used to test whether models that assume evolutionary dynamics are independent of population dynamics produce results that are robust when this assumption is relaxed. We start by applying our approach to single- and multi-locus models of host-parasite coevolution, before considering the coevolution of quantitative traits. In the single- and multi-locus models there is no separation of timescales between the ecological and evolutionary dynamics, but in the quantitative trait model we use an Adaptive Dynamics approach, which assumes a separation of timescales, although this assumption is relaxed in our simulations. We assume both populations are well mixed and that population sizes are sufficiently large to ignore the effects of drift.

CASE 1: SINGLE-LOCUS GENETICS

We begin by considering the simplest model of coevolution, where there are only two host types (x_1 and x_2) and two parasite types (y_1 and y_2), with interactions governed by a single biallelic locus (Mode 1958; Jayakar 1970; Yu 1972; Leonard 1977; Beck 1984; Frank 1991; Gandon *et al.* 1996; Table 1). Generalising the single-locus model in Segarra (2005) for different types of genetic interactions, population regulation, and so that fitness depends on the probability of encounter rather than just the frequency of each type, we define:

$$m_1^H = 1 - \beta_H z_H(P)\big(p_1 Q(x_1, y_1) + p_2 Q(x_1, y_2)(1 - c_P)\big) - \tilde{q}_H H \quad (6a)$$

$$m_2^H = (1 - c_H)\Big(1 - \beta_H z_H(P)\big(p_1 Q(x_2, y_1) + p_2 Q(x_2, y_2)(1 - c_P)\big)\Big) - \tilde{q}_H H \quad (6b)$$

$$m_1^P = \beta_P z_P(H)\big(h_1 Q(x_1, y_1) + h_2 Q(x_2, y_1)\big) - \tilde{q}_P P \quad (6c)$$

$$m_2^P = (1 - c_P)\beta_P z_P(H)\big(h_1 Q(x_1, y_2) + h_2 Q(x_2, y_2)\big) - \tilde{q}_P P \quad (6d)$$

where c_H and c_P are costs associated with types x_2 and y_2, respectively, β_H and β_P are the fitness impacts due to successful exploitation, $\tilde{q}_H$ and $\tilde{q}_P$ control the strength of additional regulation on the population through other environmental factors, and $Q(x_i, y_j)$ captures the extent to which type y_j can exploit type x_i. Fitness costs may, for example, correspond to lower baseline reproduction or transmissibility due to increased investment in resistance or infectivity traits. We consider two interaction matrices for Q: the first has $Q(x_i, y_j) = 1$ if $i = j$ and 0 otherwise, so that each host type is susceptible to one parasite type and there are no costs ($c_H, c_P = 0$) ("matching allele" genetics; Yu 1972; Seger 1988; Frank 1993); the second has $Q(x_i, y_j) = 1$ if $j \geq i$ and 0 otherwise, so that one host type is universally susceptible, one can defend itself against a single parasite type, and one parasite type can attack both host types ("gene-for-gene" genetics; Flor 1956; Jayakar 1970; Segarra 2005; Tellier & Brown 2007b).

The eco-evolutionary dynamics are given by equations (4-5). In the absence of eco-evolutionary feedbacks $(a_H, a_P = 0)$, the single locus model exhibits neutral cycles under both matching allele and gene-for-gene genetics (Fig. 1A, C; see *Supplementary Material* for detailed analysis). Yet introducing simple eco-evolutionary feedbacks $(a_H, a_P > 0)$ can have a major impact on the cycles (Fig. 1B, D; *Supplementary Material*). In the matching allele model, the internal equilibrium remains neutrally stable for the coevolutionary subsystem, but the ecological dynamics still influence the dynamics by causing the coevolutionary cycles to reduce in amplitude as the population densities, and hence the encounter rates, exhibit damped cycles. In the gene-for-gene model, the internal equilibrium is no longer neutrally stable for the coevolutionary subsystem and so both the ecological and coevolutionary dynamics exhibit damped cycles. Thus, our approach reveals that eco-evolutionary feedbacks can have a significant impact on the coevolutionary cycles in this very simple model, regardless of the underlying genetic assumptions. While a number of previous studies have found that coevolutionary cycles tend to be damped in eco-evolutionary models (Beck 1984; Ashby & Gupta 2014; Ashby & Boots 2017; MacPherson & Otto 2018), our ability to control the strength of the coupling between population and evolutionary dynamics allows us to directly examine the impact of eco-evolutionary feedbacks without changing the structure of the model. Hence we can unequivocally attribute the change in the dynamics to eco-evolutionary feedbacks rather than some other factor.

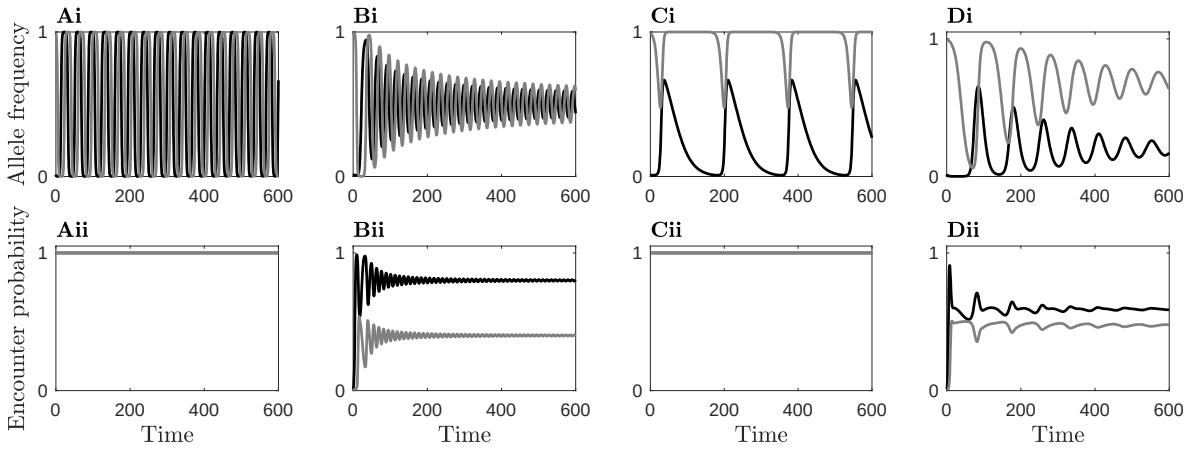

Figure 1 – Coevolutionary dynamics of the single locus model (equation 6) with (A-B) matching allele and (C-D) gene-for-gene genetics. The top row shows the frequency of host type 2 (black) and parasite type 2 (grey) alleles and the bottom row shows the encounter probability functions $z_H(P)$ (black) and $z_P(H)$ (grey). (A, C) No coupling between population and evolutionary dynamics $(a_H, a_P = 0)$ and so the encounter probability functions are constant. (B, D) Coupling between population and evolutionary dynamics using the framework described by equations (4-5), with $a_H, a_P = 1$. Other parameters: $\beta_H, \beta_P = 1$, $H_{max}, P_{max} = 1, \tilde{q}_P = 1$, $\tilde{q}_H, \tilde{q}_P = 1$, and (A-B) $c_H, c_P = 0$, (C-D) $c_H, c_P = 0.2$.

EXAMPLE 2: MULTI-LOCUS GENETICS

Our second example considers multi-locus interactions, with L biallelic loci in each species (Hamilton 1980; May & Anderson 1983; Seger 1988; Frank 1993; Parker 1994; Table 1). Genotypes are given by binary strings of length L ($x_i = X_i^1 X_i^2 \ldots X_i^L$ and $y_j = Y_j^1 Y_j^2 \ldots Y_j^L$), with $X_i^k, Y_j^k = 1$ corresponding to a defence/attack allele at locus k and $X_i^k, Y_j^k = 0$ corresponding to no defence/attack allele. We adapt the approach proposed by Sasaki (2000) and used by several others (Fenton & Brockhurst 2007; Fenton *et al.* 2009; Ashby & Boots 2017), with:

$$m_i^H = \left(1 - c_H(x_i)\right) \exp\left(-\beta_H z_H(P) \sum_{j=1}^{n_P} Q(x_i, y_j) p_j\right) - \tilde{q}_H H \tag{7a}$$

$$m_j^P = \left(1 - c_P(y_j)\right) \exp\left(\beta_P z_P(H) \sum_{i=1}^{n_h} Q(x_i, y_j) h_i\right) - \tilde{q}_P P \tag{7b}$$

where all terms as described for the single locus model and $n_H = n_P = 2^L$. The interaction matrix is defined by $Q(x_i, y_j) = \sigma^{d_{x_i y_j}}$, where σ is the reduction in susceptibility to exploitation conferred per effective defence allele, and $d_{x_i y_j} = \sum_{k=1}^{L} X_i^k (1 - Y_j^k)$ is the number of effective defence alleles (a defence allele is effective when there is no corresponding attack allele at the same locus). We set the cost functions to be identical to Sasaki (2000), with $c_H(x_i) = 1 - \mathrm{e}^{-\eta_H |x_i|}$ and $c_P(y_j) = 1 - \mathrm{e}^{-\eta_P |y_j|}$, where η_H and η_P control the strength of the trade-offs, and $|x_i|$ and $|y_j|$ are the number of defence or attack alleles for each type.

We initially seed all genotypes at random frequencies and simulate the dynamics for 2×10^4 time units, removing genotypes that have frequencies below an extinction threshold of 10^{-4}. We record the qualitative outcome and manually verify the results of a subset of the parameter space. The system is deemed to be cycling if the genotypic variance exceeds 10^{-7} during the final 10^4 time units of the simulation. Increasing or decreasing the threshold for cycling leads to slight changes along the boundary of any cycling regions, but the overall results are similar.

The eco-evolutionary dynamics are again given by equations (4-5). When $a_H, a_P = 0$ the dynamics are identical to the those described by Sasaki (2000), with only two types of outcome: cycling or stable trait monomorphism (all genotypes within a species have the same number of defence or attack alleles and coexist at the same frequency; Fig. 2A). The inclusion of eco-evolutionary feedbacks ($a_H, a_P > 0$), however, facilitates stable trait polymorphism, where genotypes with different numbers of defence or attack alleles coexist at equilibrium (Fig. 2B). This effect is consistent for non-linear encounter probabilities (Fig. S1). In addition, we find that both the propensity and nature of coevolutionary cycling

changes in the presence of eco-evolutionary feedbacks, with fluctuating dynamics less likely to occur when density-dependent effects are included (Fig. 2B). When fluctuations do occur, eco-evolutionary feedbacks tend to suppress cycling between genotypes of different ranges (i.e. with different numbers of attack or defence alleles) to a greater extent than cycling between genotypes of the same range (i.e. with the same number of attack or defence alleles) (Fig. 3). This is related to recent work showing that within- and between-range cycling can occur simultaneously or separately in the gene-for-gene model, but within-range cycles tend to be much more rapid (Ashby & Boots 2017).

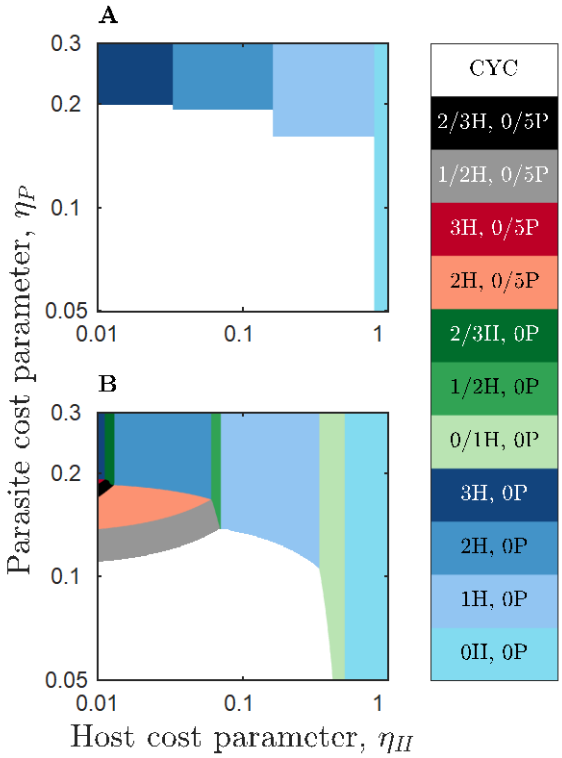

Figure 2 – Effects of eco-evolutionary feedbacks on the multilocus gene-for-gene model of host-parasite coevolution proposed by Sasaki (2000): (A) without eco-evolutionary feedbacks ($a_H, a_P = 0$); (B) with eco-evolutionary feedbacks ($a_H, a_P = 1$). Qualitatively similar outcomes are grouped by colour: blues = trait monomorphism in both populations; greens = polymorphic host traits only; reds = polymorphic parasite traits only; grey/black = both polymorphic; white = cycling. The key shows the level of investment in the host and parasite (e.g. "2/3H, 0/5P" means that hosts with 2 or 3 alleles coexist with parasites that have 0 or 5 alleles). Eco-evolutionary feedbacks facilitate trait polymorphism and generally reduce the propensity for coevolutionary cycling. Parameters: $\beta_H, \beta_P = 1$, $H_{max}, P_{max} = 1$, $L = 5$, $\tilde{q}_H = 1$, $\tilde{q}_P = e^{\beta_P}$, $\sigma = 0.2$.

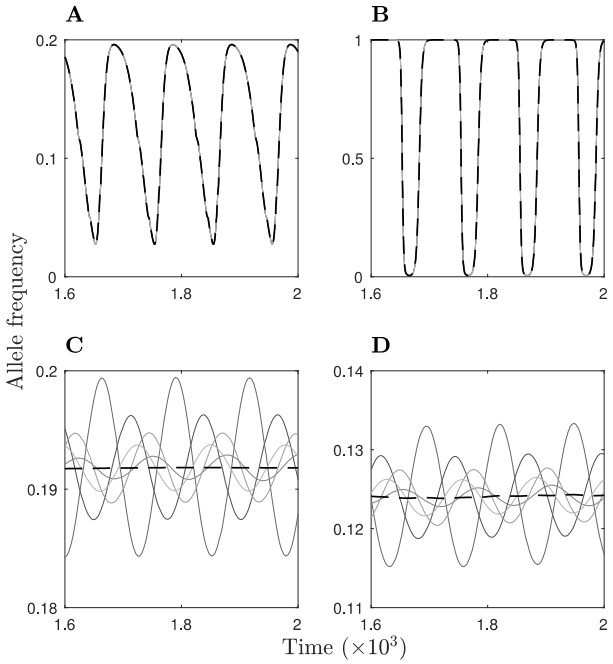

Figure 3 – Impact of eco-evolutionary feedbacks on coevolutionary cycling among (A, C) host and (B, D) parasite populations in the multi-locus gene-for-gene model: (A-B) without eco-evolutionary feedbacks ($a_H, a_P = 0$); (C-D) with eco-evolutionary feedbacks ($a_H, a_P = 1$). Grey trajectories show the frequencies of defence or attack alleles at each locus and dashed lines show the overall frequency of defence or attack alleles across all loci. Note that the grey and black trajectories overlap in panels A-B. Eco-evolutionary feedbacks tend to suppress cycling between genotypes with different numbers of defence or attack alleles to a greater extent than fluctuations among genotypes with the same number of defence or attack alleles. Parameters as described in Fig. 2, with: $\eta_H = 0.3, \eta_P = 0.1$.

EXAMPLE 3: QUANTITATIVE TRAITS

Our final example model assumes that x_i and y_j describe quantitative traits controlled by a large number of loci with additive effects between them (Table 1). We assume that the traits are bounded and discretised in the unit interval ($0 \leq x_i, y_j \leq 1$), and examine interaction functions of the form $Q(x_i, y_j) = \frac{1}{1+\exp(g(x_i - y_j))}$ and $Q(x_i, y_j) = \exp\left(-\left(\frac{x_i - y_j}{g y_j + k}\right)^2\right)$, where g and k are scaling parameters. The first function assumes that hosts and parasites vary from specialists to generalists such that $x_i = 0$ corresponds to hosts that are susceptible to attack by a wide range of parasites and $x_i = 1$ to hosts that are resistant to almost all parasites (Nuismer *et al.* 2007; Best *et al.* 2010b; Boots *et al.* 2014). The second function assumes that each parasite specialises on a particular host type (Gavrilets 1997; Nuismer *et al.* 2005; Boots *et al.* 2014), with the shape of the specialisation function dependent on the scaling parameters. Thus, parasites generally attempt to exceed the host trait in the first model (e.g. infectivity and resistance traits) and minimise the difference between the traits in the second model (e.g. avoiding non-self-recognition by hosts). These models are also sometimes referred to as a unidirectional or a bidirectional axis of vulnerability in the predator-prey literature (Abrams 2000).

We use the same core functions described for the multi-locus model (equations 7a-b) combined with the eco-evolutionary framework in equations (4-5). For simplicity, we initially focus on the situation where there is only a feedback between parasite fitness and population density ($a_P > 0, a_H = 0$, so that $0 \leq z_H(P) \leq 1, z_P(H) = 1$), but the results are similar for the converse scenario. In monomorphic resident populations (no subscript) at equilibrium (H^*, P^*), the equations for the invasion fitness of rare mutants are:

$$m_i^H = \left(1 - c_H(x_i)\right) \exp\left(-\beta_H z_H(P^*) Q(x_i, y)\right) - \tilde{q}_H H^* \tag{8a}$$

$$m_j^P = \left(1 - c_P(y_j)\right) \exp\left(\beta_P Q(x, y_j)\right) - \tilde{q}_P P^* \tag{8b}$$

The fitness gradients are then:

$$S_H = \left.\frac{dm_i^H}{dx_i}\right|_{x_i = x} = -\exp\left(-\beta_H z_H(P^*) Q(x_i, y)\right)\left(\beta_H z_H(P^*) \frac{\partial Q}{\partial x}\left(1 - c_H(x)\right) + \frac{dc_H}{dx}\right) \tag{9a}$$

$$S_P = \left.\frac{dm_j^P}{dy_j}\right|_{y_j = y} = \exp\left(\beta_P Q(x, y_j)\right)\left(\beta_P \frac{\partial Q}{\partial y}\left(1 - c_P(y)\right) + \frac{dc_P}{dy}\right) \tag{9b}$$

The populations evolve in the direction of their respective fitness gradients until a trait is either maximised, minimised, or the fitness gradient equals 0. If both $S_H = 0$ and $S_P = 0$

simultaneously at $x = x^*$ and $y = y^*$ then (x^*, y^*) is a *co-singular strategy* (co-SS) (Geritz *et al.* 1998). The *convergence stability* of a co-SS (i.e. whether or not it is locally attracting) depends on the relative rates of mutation, and so we cannot say anything general about this aspect (Leimar 2009). Instead, we consider the effects of eco-evolutionary feedbacks on evolutionary stability at the co-SS:

$$H_{ES} = \left.\frac{d^2 m_i^H}{dx_i^2}\right|_{\substack{x_i = x^* \\ y = y^*}}$$

$$= \exp\left(-\beta_H z_H(P^*) Q(x^*, y^*)\right)\left\{\beta_H z_H(P^*)\left(1 - H(x^*)\right)\left(\beta_H z_H(P^*)\left(\frac{\partial Q}{\partial x}\right)^2 - \frac{\partial^2 Q}{\partial x^2}\right) + 2\beta_H z_H(P^*)\frac{dc_H}{dx}\frac{\partial Q}{\partial x} - \frac{d^2 c_H}{dx^2}\right\} \quad (10a)$$

$$P_{ES} = \left.\frac{d^2 m_j^P}{dy_j^2}\right|_{\substack{x = x^* \\ y_j = y^*}}$$

$$= \exp\left(\beta_P Q(x^*, y^*)\right)\left\{\beta_P\left(1 - c_P(y^*)\right)\left(\beta_P\left(\frac{\partial Q}{\partial y}\right)^2 + \frac{\partial^2 Q}{\partial y^2}\right) - 2\beta_P\frac{dc_P}{dy}\frac{\partial Q}{\partial y} - \frac{d^2 c_P}{dy^2}\right\} \quad (10b)$$

where all functions are evaluated at the co-SS. When $H_{ES}, P_{ES} < 0$ the co-SS represents a local fitness maximum in each species, and when H_{ES} or $P_{ES} > 0$ the corresponding trait is at a local fitness minimum.

Clearly, the presence of an eco-evolutionary feedback can potentially affect both the existence and stability of a co-SS through the fitness gradients and shape of the local fitness landscape. Thus in principle even a simple eco-evolutionary feedback on one species is sufficient to fundamentally change the outcome of coevolution. We demonstrate this in Fig. 4 for two common models of the underlying genetic interaction, where introducing a simple eco-evolutionary feedback shifts the outcome from monomorphism to polymorphism. This occurs because the eco-evolutionary feedback results in a change in the sign of H_{ES}, causing the singular strategy for the host to switch from a fitness maximum to a fitness minimum, leading to disruptive selection. In fact, the criteria for mutual invasibility in Adaptive Dynamics, $\frac{\partial^2 m_i^H}{\partial x_i \partial x} < 0$ and $\frac{\partial^2 m_j^P}{\partial y_j \partial y} < 0$ (Geritz *et al.* 1998), tell us that evolutionary branching is impossible in the absence of an eco-evolutionary feedback, since at least one of these conditions must be satisfied as a prerequisite for evolutionary branching. In the absence of an eco-evolutionary feedback $(a_H, a_P = 0)$ population density is constant, which means the invasion fitness of a mutant is independent of the resident trait. As a result, $\frac{\partial^2 m_i^H}{\partial x_i \partial x}, \frac{\partial^2 m_j^P}{\partial y_j \partial y} = 0$ and so evolutionary branching can never occur. If there is an eco-evolutionary feedback, however, then the resident trait appears in the invasion fitness and so the cross derivative

may potentially be negative; the presence of an eco-evolutionary feedback is therefore essential for diversification due to evolutionary branching.

Finally, we apply our approach to explore how varying the strength of an eco-evolutionary feedback (a_P) affects coevolutionary dynamics. We focus on the case where hosts and parasites vary in their degree of specialism $\left(\text{i.e. a unidirectional axis: } Q(x_i, y_j) = \frac{1}{1+\exp\left(g(x_i - y_j)\right)}\right)$, as the matching (bidirectional axis) model either produces unstable cycles (Best *et al.* 2017) or branches, especially when the mutation rate is sufficiently high (Calcagno *et al.* 2010). When the parasite feedback is relatively weak ($a_P \ll 1$) the evolutionary dynamics are largely invariant to the population dynamics, whereas when the feedbacks are relatively strong the two are closely linked. We simulate coevolutionary trajectories by successively introducing a nearby mutant (differing from a resident trait by 0.01) after T timesteps. Any trait below a frequency of 10^{-4} is classed as extinct. The process is repeated until the system reaches a quasi-stable distribution of traits, or fluctuations persist for at least 10,000 iterations. The source code is available in the *Supplementary Material*. Our simulations reveal that the strength of the feedback plays a fundamental role in determining the outcome of host-parasite coevolution, with even relatively weak feedbacks leading to qualitative changes in the outcome (Fig. 5). For example, increasing the strength of the feedback can cause the evolutionary outcome to shift from monomorphism to cycling, to gradually decreasing levels of polymorphism. An important insight from this approach is that it is not just the presence or absence of an eco-evolutionary feedback that is crucial for determining the dynamics, but also its strength. These findings are consistent when the encounter probability functions are non-linear (Fig. S3) and for faster or slower mutation rates (Fig. S4).

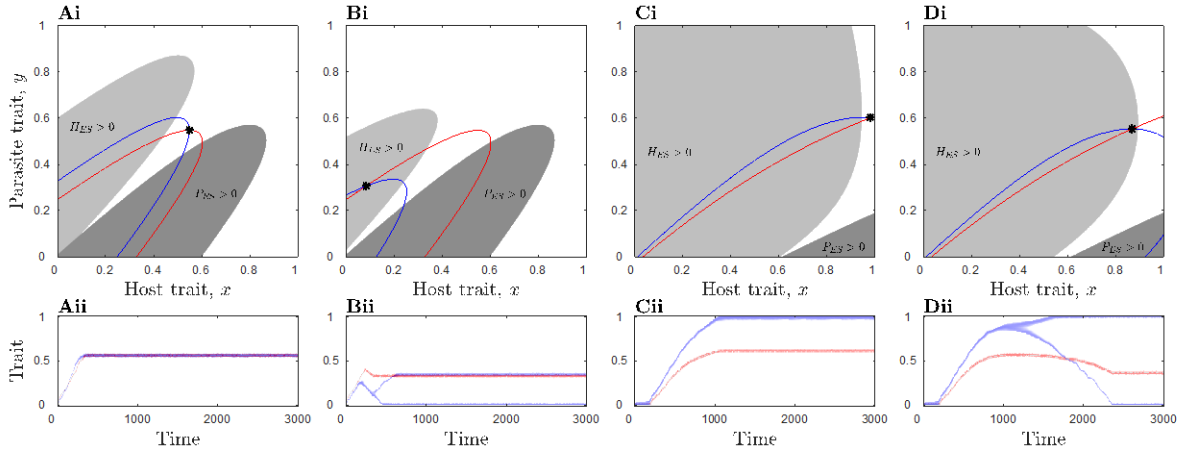

Figure 4 – Effects of a simple eco-evolutionary feedback on two common models of host-parasite coevolution: (A-B) hosts and parasites vary in their degree of specialism; (C-D) parasites specialise on a particular host type. In both models there are costs associated with greater trait values such that for population $s \in \{H, P\}$ with trait $u \in \{x, y\}$: $c_s(u) = c_s^1\left(1 - e^{c_s^2 u}\right)/(1 - e^{c_s^2})$. In (A) and (C) there are no eco-evolutionary feedbacks ($a_H, a_P = 0$), but in (B) and (D) there is a feedback on the parasite population ($a_P = 1$). The top row shows the trait space for host and parasite with blue and red curves corresponding to the nullclines for the host and parasite fitness gradients, respectively, and a star indicating a co-SS. Light and dark shading shows when the second derivatives of host and parasite invasion fitness are positive; if a co-SS is in one of these regions then it represents a fitness minimum for that species and branching may therefore occur due to disruptive selection. The bottom row shows corresponding simulations as described in the text. Parameters: $\beta_H, \beta_P = 1$, $H_{max}, P_{max} = 1$, $\tilde{q}_H = 1$, $\tilde{q}_P = e^{\beta_P}$, $T = 1000$; (A-B): $c_H^1 = 1$, $c_H^2 = 1$, $c_P^1 = 1$, $c_P^2 = 1$, $g = 7$; (C-D): $c_H^1 = 0.14$, $c_H^2 = 2.2$, $c_P^1 = 0.4$, $c_P^2 = 2$, $g = 1$, $k = 0.75$.

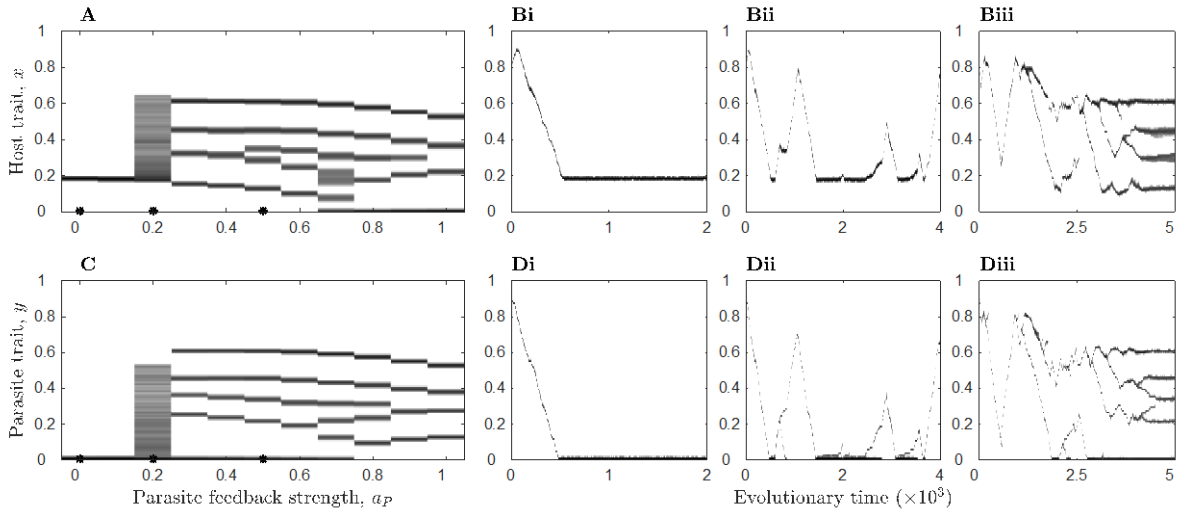

Figure 5 – Varying the strength of the eco-evolutionary feedbacks (a_H, a_P) qualitatively changes coevolutionary outcomes in the quantitative trait model (hosts and parasites vary in their degree of specialism: $Q(x_i, y_j) = \frac{1}{1+\exp(g(x_i - y_j))}$). Panels (A) and (C) show the mean frequency of host and parasite traits (following a burn-in period) as the strength of the feedbacks are varied. Panels (Bi-iii) and (Di-iii) show example coevolutionary trajectories of hosts and parasites, respectively, at the points indicated by stars in panels (A) and (C). See *Supplementary Material* for simulations with slower or faster mutation rates. Parameters and cost functions as described for Fig. 4, except: $g = 20$, $c_H^1 = 0.75$, $c_H^2 = 1$, $c_P^1 = 1$, $c_P^2 = 0.5$, and: (Bi, Di) $a_H, a_P = 0$, (Bii, Dii) $a_H, a_P = 0.2$, (Biii, Diii) $a_H, a_P = 0.5$.

DISCUSSION

It is widely recognised that ecology impacts evolution, and vice versa, yet models of host-parasite coevolution often omit population dynamics for greater tractability, hence excluding potentially important eco-evolutionary feedbacks. While a large proportion of the literature does fully account for eco-evolutionary feedbacks, there remains a significant body of theoretical research that lacks these effects by assuming population sizes are constant or infinite (Fig. S1; Table 1, S1). Here, we have proposed a method for testing the importance of this assumption by introducing simple, variable eco-evolutionary feedbacks into a wide range of non-eco-evolutionary models of host-parasite coevolution that lack these effects. It is important to note that our method is not intended to replace or replicate the dynamics of any particular eco-evolutionary model. The purpose of our method is to test whether models with fixed population sizes are robust when this assumption is relaxed and therefore whether eco-evolutionary feedbacks *per se* qualitatively affect the results, rather than trying to predict what the results would be in any given system.

It is now routine to introduce evolutionary effects into ecological models of host-parasite interactions – as is clear from the variety of methods for studying these dynamics (Dieckmann & Law 1996; Geritz *et al.* 1998; Day & Gandon 2007; Gandon & Day 2009; Nuismer 2017) – but introducing population dynamics into evolutionary models with fixed population sizes has not generally been considered. This is surprising given the large number of models that omit eco-evolutionary feedbacks (Table 1). In principle, one could test the robustness of the results from a model with fixed population sizes by comparing them to a separate eco-evolutionary model (Ashby & Boots 2017; MacPherson & Otto 2018). However, the models are unlikely to be directly comparable due to how they are structured and parameterised and therefore it may be difficult to directly attribute differences in the results due to the presence or absence of eco-evolutionary feedbacks (compare, for example, Nuismer *et al.* (2007) and Best *et al.* (2010b)). While it is relatively straightforward to introduce evolutionary effects into ecological models (since relative fitness naturally follows from differences in birth and death rates), the same is not true for introducing ecological effects into (non-eco-) evolutionary models, which typically use the replicator equations (3a-b) without explicit population dynamics as a starting point. However, the replicator equations are perfectly compatible with population dynamics, as is the case in our framework. Thus, it is possible to introduce population dynamics (and hence, eco-evolutionary feedbacks) into non-eco-evolutionary models while retaining their core structure.

Crucially, models without population dynamics assume that the encounter rates between hosts and parasites remain constant (unless the encounter rates themselves are evolving), but one must relax this assumption by allowing the functions describing fitness to depend on population sizes. In our framework we achieve this by allowing the probability of

encountering a parasite/host to vary with the density of parasites/hosts, and by allowing the population densities to be regulated by any additional environmental factors. The effects are broadly consistent whether the encounter probabilities vary linearly (Fig. 2, 5) or non-linearly (Fig. S2, S3) with population density. Although these eco-evolutionary feedbacks are only a simple approximation to the complex dynamics that exist in real populations, they capture the general patterns that one would expect to find in many host-parasite systems where encounter rates increase with population density (e.g. encounter rates are proportional to abundance under mass-action kinetics). Future work could extend the current model to capture alternative contact processes, such as frequency-dependent transmission (Hethcote & Yorke 1984). Despite its simplicity, the major advantage of our approach is that it allows us to introduce eco-evolutionary feedbacks without changing anything else in the underlying model, so that one can directly attribute changes in the results to eco-evolutionary feedbacks as opposed to other factors (e.g. model structure, parameterisation, etc).

Another assumption of our modelling framework is that host and parasite fitness can be decomposed into components characterising the host-parasite interaction and external regulating factors such as predation or resource limitation. We did this because it meant that any external population regulation effects did not structurally change the replicator equations, with any effects instead mediated through the encounter probability functions. As such, we could directly attribute any changes in the evolutionary dynamics to eco-evolutionary feedbacks themselves rather than structural changes to the underlying replicator equations. Although one may not be able to fully decompose these effects in real populations, the purpose of our study is to propose a method for testing whether the assumption of constant population sizes is robust, and therefore we simply have to test whether eco-evolutionary feedbacks *per se* affect the outcome of host-parasite coevolution in these models. Still, it would be worth investigating further developments of our framework whereby internal and external regulating effects are not combined additively.

To demonstrate the utility of our framework we applied it to a variety of models of host-parasite coevolution, from single- and multi-locus genetics to quantitative traits. In all cases, we found that introducing or varying the strength of eco-evolutionary feedbacks can lead to qualitatively different coevolutionary outcomes. For example, in the most basic single locus model eco-evolutionary feedbacks can cause the coevolutionary cycles to be damped. Similarly, applying our framework to the multi-locus gene-for-gene model proposed by Sasaki (2000) revealed that eco-evolutionary feedbacks: (1) lead to stable trait polymorphism; (2) reduce the likelihood of coevolutionary cycling; and (3) change the nature of the cycles so that fluctuations tend to occur among genotypes with the same rather than different numbers of defence/attack alleles. The latter outcome is referred to by Ashby & Boots (2017) as ‘within-range’ rather than ‘between-range’ cycling, and

corresponds more closely to the dynamics of classical matching allele models. Finally, we showed that varying the strength of the eco-evolutionary feedbacks qualitatively changes coevolutionary dynamics in a model with quantitative traits, causing shifts between monomorphism, cycling, and polymorphism, as well as changes in the extent of polymorphism (the number of coexisting types). Varying the strength of the eco-evolutionary feedbacks is equivalent to controlling the degree to which the encounter probabilities depend on population densities, which allows us to capture a range of different biological scenarios. In some cases, the results may hold for relatively weak eco-evolutionary feedbacks and only change when the feedbacks are moderately strong. However, there is a discontinuity in our model in terms of whether the feedbacks are present ($a_H, a_P > 0$) or absent ($a_H, a_P = 0$), and in principle even an arbitrarily weak feedback could qualitatively change the results. For example, the criteria for mutual invasibility (a prerequisite for evolutionary branching) in Adaptive Dynamics is sign-dependent, rather than magnitude-dependent (Geritz *et al.* 1998). In the absence of eco-evolutionary feedbacks, this term is always equal to zero, but could be negative in the presence of an arbitrarily weak feedback, and hence there may be a discontinuity in the dynamics. This means that even if one suspects that eco-evolutionary feedbacks are very weak in a particular system, they could still affect the results. Overall, the examples we have chosen, which primarily served as demonstrations for how to apply our approach, show that eco-evolutionary feedbacks likely play an important role in host-parasite coevolution regardless of the underlying genetics.

Our approach for introducing eco-evolutionary feedbacks is not intended to be a starting point for constructing an eco-evolutionary model of coevolution – ideally one should start from an underlying ecological model and facilitate evolution by introducing multiple types to the population – but is instead a means to test whether the results of non-eco-evolutionary models are robust when population dynamics are included. A number of recent studies have taken similar approaches to test whether results are robust when population sizes are allowed to fluctuate, with a particular focus on non-equilibrium dynamics. For example, Gokhale *et al.* (2013) adapted a Lotka-Volterra model to have fixed population sizes by resetting the total number of hosts and parasites to their initial values after every generation while maintaining the relative frequencies of each allele. When combined with stochasticity, the authors found that coevolutionary cycling was unlikely to be maintained if population sizes were allowed to fluctuate. Similarly, Song *et al.* (2015) set the birth and death rates in the Lotka-Volterra model to be dynamic so as to maintain constant population sizes, which led to more complex cycles than when population sizes were variable. MacPherson & Otto (2018) have also recently compared the coevolutionary dynamics of two separate models where population sizes are either fixed or variable, finding that cycles are likely to be damped in the latter, although parasitic castration has previously been shown to allow cycling to persist in an eco-evolutionary setting (Ashby & Gupta 2014). These studies are in broad agreement with our own findings, namely that eco-evolutionary

feedbacks tend to fundamentally change the nature of coevolutionary cycling. The impact of eco-evolutionary feedbacks on coevolutionary cycling is critically important for the evolutionary maintenance of sex (the "Red Queen Hypothesis" for sex, Bell (1982)), since these dynamics are the key factor selecting for sex in most models (Lively 2010a), yet population dynamics are typically absent (although see: May & Anderson 1983; Lively 2010b; Ashby & Gupta 2014; Ashby & King 2015). Our framework offers a straightforward means of testing whether selection for sex in these models still occurs when population dynamics are present.

In principle, our method for introducing variable eco-evolutionary feedbacks could be readily applied to non-coevolutionary systems (e.g. the evolution of host resistance in a non-evolving parasite population) or other inter/intraspecific interactions where potential feedbacks between population and evolutionary dynamics have been omitted, such as predator-prey relationships, mutualisms, and sexual antagonism. We framed our study in the context of host-parasite coevolution because there are a large number of theoretical studies in this section of the literature which lack eco-evolutionary feedbacks. In contrast, studies of predator-prey systems typically include eco-evolutionary feedbacks (Marrow *et al.* 1992, 1996; Dieckmann *et al.* 1995; Abrams & Matsuda 1996; Abrams 2000; Waltman *et al.* 2002; Yoshida *et al.* 2003; Cortez & Ellner 2010; Cortez & Weitz 2014; Yamamichi & Ellner 2016), perhaps owing to the long history of the Lotka-Volterra equations in evolutionary ecology (Lotka 1925; Volterra 1926). In fact, many eco-evolutionary studies of host-parasite interactions assume that infected hosts do not recover or reproduce (Gokhale et al. 2013; Rabajante et al. 2015; Song et al. 2015), in which case the dynamics may reduce to the Lotka-Volterra equations (Ashby & Gupta 2014).

While eco-evolutionary feedbacks will not always have a significant effect on host-parasite coevolutionary dynamics (Ashby & Boots 2017; Nuismer 2017), our results, together with those from a number of other recent studies (Gokhale *et al.* 2013; Song *et al.* 2015; MacPherson & Otto 2018) suggest that they can play a crucial role.

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AUTHOR CONTRIBUTIONS

BA and MB conceived the study and wrote the first draft of the manuscript. BA and RI analysed the theoretical models. All authors contributed to revisions of the manuscript.

DATA ACCESSIBILITY

Simulation code is available in the *Supplementary Material* at doi:10.1016/j.jtbi.2018.12.031.

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Supplementary material: Understanding the role of eco-evolutionary feedbacks in host-parasite coevolution

S1. Details of the literature analysis

We searched the PubMed database using the following query:

(model* OR simulation* OR theory OR theoretical OR mathematical) AND (coevolution* OR co-evolution* OR coevolve* OR co-evolve* OR (red AND queen)) AND (host* OR parasite* OR pathogen*) AND ("2000"[Date - Publication] : "2017"[Date - Publication]).

The search returned a total of 1058 studies, 9 of which were removed from further analysis due to erroneous publication dates. Of the remaining 1049 studies, 185 were found to include a theoretical model of host-parasite coevolution (determined through manual inspection of each study). These studies were then categorised according to whether both host and parasite populations were dynamic or if one or more population size was fixed (summary results in Table S1, Fig. S1). Raw search data and breakdown of the analysis are shown in a separate file.

Publication year	Number of studies	Percentage of studies without host and/or parasite population dynamics
2000	4	75.00%
2001	3	66.67%
2002	5	40.00%
2003	10	50.00%
2004	3	100.00%
2005	6	66.67%
2006	6	83.33%
2007	10	90.00%
2008	8	62.50%
2009	16	56.25%
2010	6	33.33%
2011	7	57.14%
2012	12	66.67%
2013	15	53.33%
2014	17	47.06%
2015	18	27.78%
2016	12	41.67%
2017	25	44.00%
Total	**183**	75.00%

Table S1 – Results of the literature analysis.

S2. Stability analysis for the single locus model

The fitness functions for the single locus model are given by equation (6) in the main text. The population and evolutionary dynamics are given by:

$$\frac{dH}{dt} = \bar{m}_H H \tag{S1a}$$
$$\frac{dP}{dt} = \bar{m}_P P \tag{S1b}$$
$$\frac{dh}{dt} = h(m_1^H - \bar{m}_H) \tag{S1c}$$
$$\frac{dp}{dt} = p(m_1^P - \bar{m}_P) \tag{S1d}$$

In the absence of eco-evolutionary feedbacks, the evolutionary dynamics are independent of equations (S1a-b), in which case the Jacobian is:

$$J = \begin{pmatrix} (1-2h)(m_1^H - m_2^H) & h(1-h)\left(\frac{\partial m_1^H}{\partial p} - \frac{\partial m_2^H}{\partial p}\right) \\ p(1-p)\left(\frac{\partial m_1^P}{\partial h} - \frac{\partial m_2^P}{\partial h}\right) & (1-2p)(m_1^P - m_2^P) \end{pmatrix} \tag{S2}$$

In the matching allele model, the internal equilibrium occurs at $(h^*, p^*) = \left(\frac{1}{2}, \frac{1}{2}\right)$. The leading diagonal elements of J therefore disappear and the eigenvalues are:

$$\lambda = \pm\frac{1}{4}\sqrt{\left(\frac{\partial m_1^H}{\partial p} - \frac{\partial m_2^H}{\partial p}\right)\left(\frac{\partial m_1^P}{\partial h} - \frac{\partial m_2^P}{\partial h}\right)} \tag{S3}$$

with the derivatives evaluated at (h^*, p^*). The terms $\left(\frac{\partial m_1^H}{\partial p} - \frac{\partial m_2^H}{\partial p}\right)$ and $\left(\frac{\partial m_1^P}{\partial h} - \frac{\partial m_2^P}{\partial h}\right)$ have opposite signs, which means the eigenvalues are imaginary and hence the system exhibits neutrally stable cycles.

In the gene-for-gene model with costs the internal equilibrium, which exists for $\beta_H > c_H$, occurs at

$$(h^*, p^*) = \left(1 - c_P, \frac{c_H(1 - \beta_H(1 - c_P))}{\beta_H(1 - c_H(1 - c_P))}\right) \tag{S4}$$

and the eigenvalues are

$$\lambda = \pm\sqrt{\frac{c_H c_P \beta_P (1-c_P)(c_H-\beta_H)(1-(1-c_P)\beta_H)}{\beta_H\big(1-c_H(1-c_P)\big)}} \qquad (S5)$$

which are imaginary and hence this system also exhibits neutrally stable cycles.

We now introduce eco-evolutionary feedbacks by setting $z_H(P) = P$ and $z_P(H) = H$ in equation (6) in the main text. This means that the evolutionary dynamics of equation (S1c-d) depend on the ecological dynamics in equation (S1a-b). The Jacobian is then given by:

$$J = \begin{pmatrix} J_{11} & J_{12} \\ J_{21} & J_{22} \end{pmatrix} \qquad (S6)$$

where

$$J_{11} = \begin{pmatrix} H\left(h\frac{\partial m_1^H}{\partial H} + (1-h)\frac{\partial m_2^H}{\partial H}\right) + hm_1^H + (1-h)m_2^H & H\left(h\frac{\partial m_1^H}{\partial P} + (1-h)\frac{\partial m_2^H}{\partial P}\right) \\ P\left(p\frac{\partial m_1^P}{\partial H} + (1-p)\frac{\partial m_2^P}{\partial H}\right) & P\left(p\frac{\partial m_1^P}{\partial P} + (1-p)\frac{\partial m_2^P}{\partial P}\right) + pm_1^P + (1-p)m_2^P \end{pmatrix} \qquad (S7a)$$

$$J_{12} = \begin{pmatrix} H(m_1^H - m_2^H) & H\left(h\frac{\partial m_1^H}{\partial p} + (1-h)\frac{\partial m_2^H}{\partial p}\right) \\ P\left(p\frac{\partial m_1^P}{\partial h} + (1-p)\frac{\partial m_2^P}{\partial h}\right) & P(m_1^P - m_2^P) \end{pmatrix} \qquad (S7b)$$

$$J_{21} = \begin{pmatrix} h(1-h)\left(\frac{\partial m_1^H}{\partial H} - \frac{\partial m_2^H}{\partial H}\right) & h(1-h)\left(\frac{\partial m_1^H}{\partial P} - \frac{\partial m_2^H}{\partial P}\right) \\ p(1-p)\left(\frac{\partial m_1^P}{\partial H} - \frac{\partial m_2^P}{\partial H}\right) & p(1-p)\left(\frac{\partial m_1^P}{\partial P} - \frac{\partial m_2^P}{\partial P}\right) \end{pmatrix} \qquad (S7c)$$

and J_{22} is equal to equation (S2).

In the matching allele model, the internal equilibrium occurs at

$$(H^*, P^*, h^*, p^*) = \left(\frac{4q_P}{\beta_H\beta_P + 4q_Hq_P}, \frac{2\beta_P}{\beta_H\beta_P + 4q_Hq_P}, \frac{1}{2}, \frac{1}{2}\right) \qquad (S8)$$

at which point the matrices J_{12} and J_{21} are zero. The eigenvalues are given by:

$$\lambda_{1,2} = \frac{-q_P(\beta_P + 2q_H) \pm 2\sqrt{q_P\left(q_P\left(q_H - \frac{\beta_P}{2}\right)^2 - \frac{\beta_H\beta_P^2}{2}\right)}}{\beta_H\beta_P + 4q_Hq_P} \qquad (S9a)$$

$$\lambda_{3,4} = \pm\frac{\beta_P\sqrt{-2q_H\beta_H}}{\beta_H\beta_P + 4q_Hq_P} \qquad (S9b)$$

The first two eigenvalues, $\lambda_{1,2}$, correspond to the ecological dynamics near the internal equilibrium, and the latter two, $\lambda_{3,4}$, to the coevolutionary dynamics. Since $\lambda_{3,4}$ are imaginary, this implies that the long-term coevolutionary dynamics are neutrally stable cycles. However, the ecological dynamics are stabilising, which ultimately has a damping effect on the amplitude of the coevolutionary cycles until the population densities reach equilibrium (Fig. 1B).

In the gene-for-gene model, the internal equilibrium, (H^*, P^*, h^*, p^*), occurs at

$$\left(\frac{q_P(1-c_H)}{K_0}, \frac{\beta_P(1-c_H)(1-c_P)}{K_0}, 1-c_P, \frac{c_H q_H q_P}{\beta_H \beta_P (1-c_H)(1-c_P)}\right) \quad (S10)$$

where $K_0 = \beta_P(1-c_P)^2(1-c_H)\beta_H + q_H q_P\big(1-c_H(1-c_P)\big)$. Substituting in the parameter values from Fig. 1, we find that all 4 eigenvalues are complex with negative real parts. Since the first two eigenvalues correspond to the ecological dynamics and the latter two to the evolutionary dynamics, this means that both exhibit damped cycles, as shown in Fig. 1D.

S3. Non-linear encounter probabilities

In the main text we assume that the encounter probability functions, $z_H(P)$ and $z_P(H)$, which are used to introduce eco-evolutionary feedbacks to the models, vary linearly with population density. Here, we show that the effects are broadly similar when these functions are non-linear by setting:

$$z_H(P) = a_P\left(\frac{P}{P_{max}}\right)^{b_P} + (1-a_P) \quad (S11a)$$

$$z_P(H) = a_H\left(\frac{H}{H_{max}}\right)^{b_H} + (1-a_H) \quad (S11b)$$

where $b_H > 0$ and $b_P > 0$ control the shape of the relationships between relative population density and encounter rate. Using these functions, we run simulations as described in the main text for the multi-locus (Fig. S2) and quantitative trait (Fig. S3) models (compare with Fig. 2B and Fig. 5A, 5C, respectively).

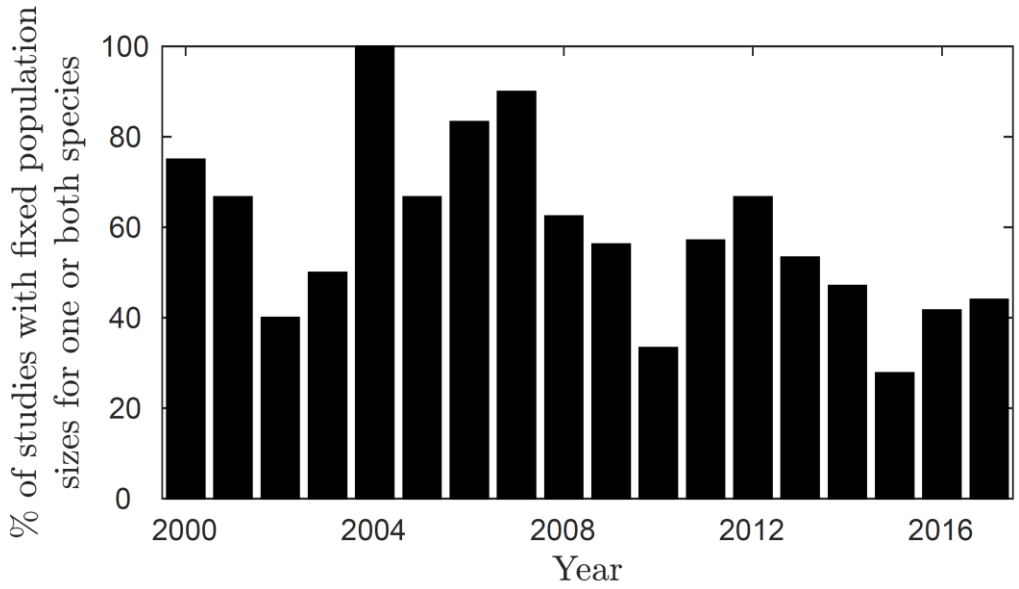

Figure S1 – Results of the literature analysis, showing the percentage of studies published per year featuring models of host-parasite coevolution (n=183) that assume fixed population sizes for one (n=3) or both (n=95) species.

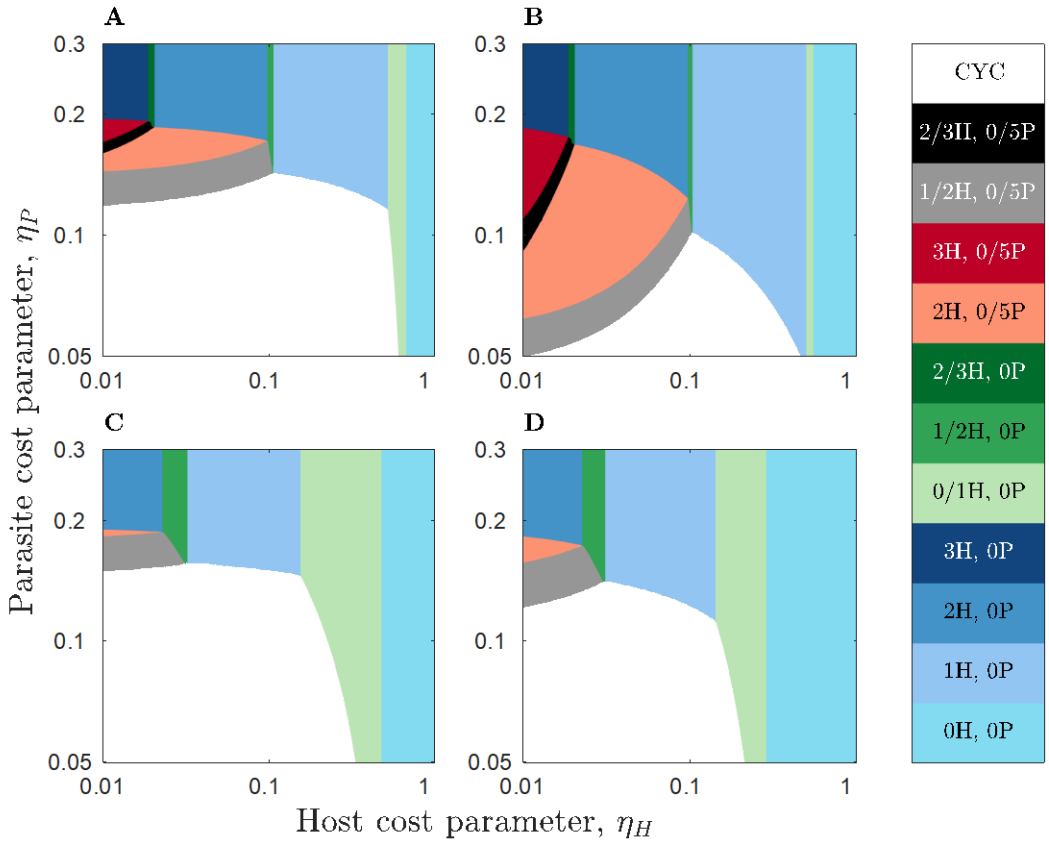

Figure S2 – Effects of eco-evolutionary feedbacks on the multilocus gene-for-gene model of host-parasite coevolution described in the main text, with non-linear encounter probabilities (equation S11). Qualitatively similar outcomes are grouped by colour: blues = trait monomorphism in both populations; greens = polymorphic host traits only; reds = polymorphic parasite traits only; grey/black = both polymorphic; white = cycling. The key shows the level of investment in the host and parasite (e.g. "2/3H, 0/5P" means that hosts with 2 or 3 alleles coexist with parasites that have 0 or 5 alleles). Eco-evolutionary feedbacks facilitate trait polymorphism and generally reduce the propensity for coevolutionary cycling. Other parameters: $a_H, a_P = 1$, $\beta_H, \beta_P = 1$, $L = 5$, $\tilde{q}_H = 1$, $\tilde{q}_P = e^{\beta_P}$, $\sigma = 0.2$, and: (A) $b_H = 0.5, b_P = 0.5$; (B) $b_H = 2, b_P = 0.5$; (C) $b_H = 2, b_P = 0.5$; (D) $b_H = 2, b_P = 2$.

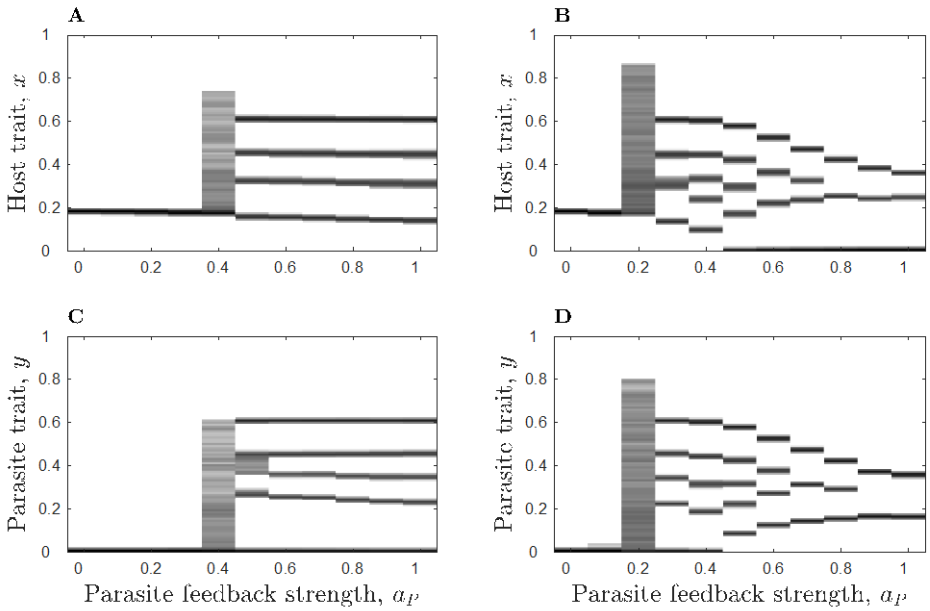

Figure S3 – Analysis of the quantitative trait model with non-linear encounter probabilities (equation S11). Hosts and parasites vary in their degree of specialism, as described in Fig. 5. Panels (A) and (B) show the mean frequency of host traits and panels (C) and (D) show the mean frequency of parasite traits (following a burn-in period) as the strength of the parasite feedback is varied. Parameters and cost functions as described for Fig. 5, with $b_H = 1$ and: (A, C) $b_P = 1/3$; (B, D) $b_P = 3$.

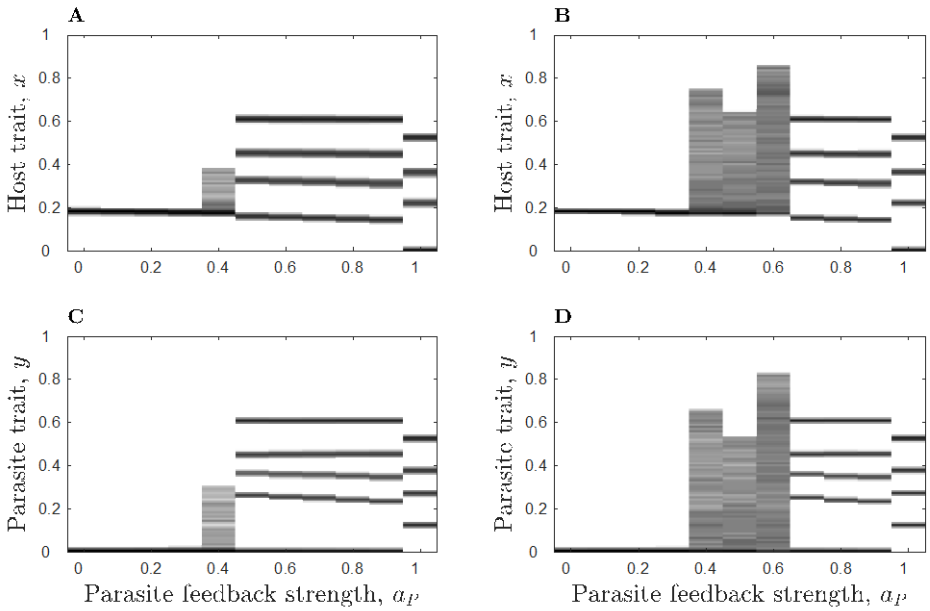

Figure S4 – Analysis of the quantitative trait model with linear encounter probabilities and (A,C) faster or (B, D) slower mutation rates. Hosts and parasites vary in their degree of specialism, as described in Fig. 5. Panels (A) and (B) show the mean frequency of host traits and panels (C) and (D) show the mean frequency of parasite traits (following a burn-in period) as the strength of the parasite feedback is varied. Parameters and cost functions as described for Fig. 5, with $b_H = 1$, $b_P = 1/3$ and: (A, C) $T = 500$; (B, D) $T = 2000$.