Separation of evolutionary timescales in coevolving species

Lydia J. Buckingham[1,2,*] and Ben Ashby[1,2,3,4]

1. Department of Mathematical Sciences, University of Bath, Bath, UK
2. Milner Centre for Evolution, University of Bath, Bath, UK
3. Department of Mathematics, Simon Fraser University, Burnaby, BC, Canada
4. The Pacific Institute on Pathogens, Pandemics and Society (PIPPS), Simon Fraser University, Burnaby, BC

*Corresponding author: ljb74@bath.ac.uk

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ABSTRACT

Many coevolutionary processes, including host-parasite and host-symbiont interactions, involve one species or trait which evolves much faster than the other. Whether or not a coevolutionary trajectory converges depends on the relative rates of evolutionary change in the two species, and so current adaptive dynamics approaches generally either determine convergence stability by considering arbitrary (often comparable) rates of evolutionary change or else rely on necessary or sufficient conditions for convergence stability. We propose a method for determining convergence stability in the case where one species is expected to evolve much faster than the other. This requires a second separation of timescales, which assumes that the faster evolving species will reach its evolutionary equilibrium (if one exists) before a new mutation arises in the more slowly evolving species. This method, which is likely to be a reasonable approximation for many coevolving species, both provides straightforward conditions for convergence stability and is less computationally expensive than traditional analysis of coevolution models, as it reduces the trait space from a two-dimensional plane to a one-dimensional manifold. In this paper, we present the theory underlying this new separation of timescales and provide examples of how it could be used to determine coevolutionary outcomes from models.

INTRODUCTION

Coevolution is ubiquitous in nature and has been implicated in many biological phenomena, including diversification (Futuyma and Agrawal, 2009; Paterson et al., 2010; Thompson, 2009) and the evolution of sex (Hamilton et al., 1990; Morran et al., 2011). Coevolving species may be mutualistic, such as host-symbiont (Janzen, 1966; Limborg and Heeb, 2018) or plant-pollinator (Johnson and Anderson, 2010) relationships; antagonistic, such as host-parasite (Flor, 1956; Marshall and Fenner, 1960, 1958) (including brood parasitism (Feeney et al., 2014)) or predator-prey (Heiling and Herberstein, 2004; Vermeij and Covich, 1978) (including herbivory (Ehrlich and Raven, 1964)) relationships; or competitive (Leger and Espeland, 2010). Coevolution can lead to rapid reciprocal adaptations, but in many cases species evolve at very different rates, especially when interactions occur across trophic levels (e.g. plant or animal interactions with microbial species (Drew et al., 2021)).

For example, bacterial or fungal symbionts typically evolve much faster than their hosts (Moran et al., 1995) and viral or bacterial parasites have generation times and population sizes that are orders of magnitude faster or larger than their plant or animal hosts, setting the stage for much faster adaptive evolution (Bliven and Maurelli, 2016; Elena et al., 2008). This includes RNA viruses of humans, such as coronaviruses and influenza viruses, which typically have generation times measured in hours with tens of billions of virions per infection, whereas humans have generation times measured in decades with fewer individuals in the entire human population than virions in a single infected host (Bar-On et al., 2020; Sender et al., 2021). Of course, vertebrates can keep pace with many parasites through adaptive immunity, which in many cases is the more pertinent driver of parasite evolution over shorter timescales, but over longer timescales parasites can drive evolution in vertebrate

populations, leading to coevolution between a host and a much faster evolving microbe. Beyond host-microbe interactions, contrasting generation times and population sizes occur in a wide range of other ecological relationships, including plant-herbivore (e.g. insect herbivores have much shorter lifespans and so evolve much faster than long-lived trees (Edmunds and Alstad, 1978; Karban, 1989)), predator-prey (e.g. krill and whales (Jarman, 2001; Meredith et al., 2013; Pyenson, 2017)) and competitive interactions (e.g. fast evolving algae compete for space with more slowly evolving corals (Swierts and Vermeij, 2016)).

One can employ a variety of methods to model coevolutionary dynamics theoretically (Ashby et al., 2019; Buckingham and Ashby, 2022), including population genetics (Day and Gandon, 2007), quantitative genetics (Nuismer et al., 2007), adaptive dynamics (Dieckmann and Law, 1996; Geritz et al., 1998; Kisdi, 2006; Metz et al., 1995) and oligomorphic dynamics (Sasaki and Dieckmann, 2011). Adaptive dynamics (also known as evolutionary invasion analysis) is especially useful for modelling the long-term evolutionary dynamics of quantitative traits, as it naturally incorporates population (ecological) dynamics and is relatively straightforward to implement. A key assumption of this method is a separation of ecological and evolutionary timescales, so that the system reaches its ecological attractor (usually a stable equilibrium or limit cycle (Best and Ashby, 2023)) before a new mutation arises. This greatly simplifies the analysis because ecological dynamics (for instance, changes in population density) can be considered separately to evolutionary (trait) dynamics. However, important feedbacks remain between the ecological and evolutionary dynamics that play a fundamental role in shaping coevolution (Ashby et al., 2019). Separating evolutionary and ecological timescales is also a reasonable approximation for many real biological systems, as evolutionary dynamics are often, but not always (Pelletier et al., 2009), much slower than ecological dynamics.

Here, we generalise and elaborate on a recent method for separating evolutionary timescales in coevolving species (Ashby and Farine, 2022). We propose that for systems where one species typically evolves much faster than the other (e.g., due to stark differences in generation times, population sizes or mutation rates) one can reasonably introduce a second separation of timescales between the evolutionary dynamics of the two species. This greatly simplifies the analysis by collapsing coevolutionary dynamics in a two-dimensional plane into a one-dimensional manifold. In this paper, we will describe this method for modelling the coevolution of two species and consider how the results compare to existing adaptive dynamics methods.

METHODS

We begin by outlining the classical adaptive dynamics framework for two coevolving species, before introducing an approximation using a separation of evolutionary timescales between species. For convenience, we will use the example of a host-parasite system throughout, although these methods may be applied to many other coevolving species. Thus, “parasite” may be used interchangeably with “fast evolving species” and “host” with “slowly evolving species”. This method could also be applied to two coevolving traits within the same species, as long as one evolves much faster than the other. Note that the rates of evolutionary change in each species will depend on the size and frequency of mutations, population sizes and the selection gradient. Here, when we refer to a fast evolving species (e.g., a parasite), we mean that these factors combine to give a much higher rate of evolutionary change than in the slowly evolving species.

ADAPTIVE DYNAMICS FOR COEVOLVING SPECIES

The adaptive dynamics framework for two coevolving, asexual species has been described in detail elsewhere (Dieckmann and Law, 1996; Geritz et al., 1998; Kisdi, 2006; Metz et al., 1995), so here we shall only give a brief overview. The framework makes two crucial assumptions. First, that there is a separation of ecological and evolutionary timescales, such that a mutation may only occur after the ecological dynamics have reached an attractor (e.g. an equilibrium or a limit cycle). In other words, selection acts relatively quickly so that the fate of a mutant is determined before another mutant arises. Second, mutations are assumed to have small additive effects, which means that traits are modelled as continuous with mutants phenotypically similar to their progenitors. Note that even though traits are modelled as continuous, mutation effect sizes are assumed to be small but not infinitesimal. This allows for outcomes such as evolutionary branching, which cannot occur if mutations have infinitesimal effects (Geritz et al., 1998).

For (initially) monomorphic host (H) and parasite (P) populations, with evolvable traits h and p respectively, the invasion fitness of a rare mutant h_m or p_m is given by a function of the form $w_H(h_m, h, p)$ or $w_P(p_m, h, p)$, where the current resident population determines the "environment" that the mutant experiences. The traits evolve in the direction of their respective fitness gradients, $s_H(h,p) = \left.\frac{\partial w_H}{\partial h_m}\right|_{h_m=h}$ and $s_p(h,p) = \left.\frac{\partial w_P}{\partial p_m}\right|_{p_m=p}$, until a pair of *co-singular strategies* $(h^*,\ p^*)$ are reached, which satisfy $s_H(h^*, p^*) = s_P(h^*, p^*) = 0$. The stability of a pair of co-singular strategies is determined both in terms of *evolutionary stability*, which tells us whether a rare mutant can invade, and by *convergence stability*, which tells us

whether trait values that are sufficiently close to (h^*, p^*) will tend towards this point in the long-term. A pair of co-singular strategies is evolutionarily stable for the host if:

$$\left.\frac{\partial^2 w_H}{\partial h_m^2}\right|_{\substack{h_m=h=h^* \\ p=p^*}} < 0 \qquad (1a)$$

and is evolutionarily stable for the parasite if:

$$\left.\frac{\partial^2 w_P}{\partial p_m^2}\right|_{\substack{h=h^* \\ p_m=p=p^*}} < 0 \qquad (1b)$$

Though convergence stability is relatively straightforward to calculate when there is only one evolving trait, it is more difficult when there are two or more traits because convergence stability depends on the relative rates of evolutionary change (Geritz et al., 1998; Kisdi, 2006). In simple systems, one may derive sufficient, but not necessary, conditions for convergence. For example, *strong convergence stability* (Leimar, 2009) is the property whereby every coevolutionary trajectory with sufficiently small mutational steps will converge to a pair of co-singular strategies. Specifically, co-singular strategies are strongly convergence stable if the following three conditions all hold:

$$\frac{\partial^2 w_H}{\partial h_m^2} + \frac{\partial^2 w_H}{\partial h_m \partial h} < 0 \qquad (2a)$$

$$\frac{\partial^2 w_P}{\partial p_m^2} + \frac{\partial^2 w_P}{\partial p_m \partial p} < 0 \qquad (2b)$$

$$\left(\frac{\partial^2 w_H}{\partial h_m^2} + \frac{\partial^2 w_H}{\partial h_m \partial h}\right)\left(\frac{\partial^2 w_P}{\partial p_m^2} + \frac{\partial^2 w_P}{\partial p_m \partial p}\right) > \frac{\partial^2 w_H}{\partial h_m \partial p}\frac{\partial^2 w_P}{\partial p_m \partial h} \qquad (2c)$$

where all derivatives are evaluated at the co-singular strategies ($h_m = h = h^*$ and $p_m = p = p^*$). Since this is a sufficient, but not necessary, set of conditions for convergence to (h^*, p^*), a pair of co-singular strategies may not be strongly convergence stable even if many coevolutionary trajectories still converge to it. A pair of co-singular strategies which is

convergence stable and evolutionarily stable for both the host and parasite is called a *co-continuously stable strategy* (co-CSS).

SEPARATION OF HOST AND PARASITE EVOLUTIONARY TIMESCALES

In systems where the rate of evolutionary change in one species (e.g., a parasite) is much faster than the other (e.g., a host), we can make a second separation of timescales, between host and parasite evolutionary dynamics. We therefore have ecological dynamics occurring on a much faster timescale than parasite evolution, which in turn occurs on a much faster timescale than host evolution. This is a reasonable assumption for many host-parasite interactions, where parasite population sizes and generation times may be many orders of magnitude larger and shorter, respectively, than in the host. We therefore assume that, for a given value of the host trait h, the parasite reaches an evolutionary attractor (if one exists) before the next host mutation occurs.

A singular strategy for the parasite (if one or more singular strategies exist) as a function of the host trait, $\tilde{p}(h)$, is now found by solving:

$$s_P\big(h, \tilde{p}(h)\big) = 0 \tag{3}$$

Such a singular strategy is then evolutionarily stable for the parasite if:

$$\left.\frac{\partial^2 w_P}{\partial p_m^2}\right|_{p_m = p = \tilde{p}(h)} < 0 \tag{4}$$

and is convergence stable if:

$$\left.\frac{\partial^2 w_P}{\partial p_m^2}\right|_{p_m = p = \tilde{p}(h)} + \left.\frac{\partial^2 w_P}{\partial p_m \partial p}\right|_{p_m = p = \tilde{p}(h)} < 0 \tag{5}$$

Note that these conditions depend on the host trait value, h, but do not depend on the rate of evolutionary change in the host, due to the second separation of timescales.

For a given value of the host trait, the long-term trait dynamics of a fast-evolving parasite may be: (1) a monomorphic population that tends to a continuously stable strategy or a maximum or minimum trait value; (2) a polymorphic population arising from evolutionary branching into two or more traits, which tend to a set of continuously stable strategies, and/or maximum or minimum trait values; (3) directional selection in one or more trait values that tend to positive or negative infinity; (4) fluctuating selection in one or more trait values (e.g., due to seasonality in the ecological dynamics); (5) drift or (6) extinction of one or both populations. Here, we focus on scenarios 1-2, as scenarios 3-5 represent non-equilibrium evolutionary dynamics for the parasite (and may therefore require consideration of Floquet exponents (Ferriere and Fox, 1995; Ferriere and Gatto, 1995; Geritz et al., 2007; Klausmeier, 2008) or stochasticity) and scenario 6 is trivial as extinction of one or both species prevents further coevolution.

SCENARIO 1: MONOMORPHIC PARASITE POPULATION

Suppose that the parasite remains monomorphic and tends to either a continuously stable strategy (CSS; if $\tilde{p}(h)$ is evolutionarily stable and convergence stable), or a maximum or minimum trait value (if the fitness gradient at a boundary points towards the boundary). We denote the evolved parasite trait by $\hat{p}(h)$ (note that in the case of a CSS, $\hat{p}(h) = \tilde{p}(h)$).

The invasion fitness of a rare host mutant is then given by $\widehat{w}_H(h_m, h) = w_H\big(h_m, h, \hat{p}(h)\big)$, with fitness gradient $\hat{s}_H\big(h, \hat{p}(h)\big) = \left.\frac{\partial \widehat{w}_H}{\partial h_m}\right|_{\substack{h_m=h \\ p=\hat{p}(h)}}$ The host singular strategy therefore satisfies $\hat{s}_H\big(h^*, \hat{p}(h^*)\big) = 0$, and is evolutionarily stable if:

$$\left.\frac{\partial^2 \widehat{w}_H}{\partial h_m^2}\right|_{\substack{h_m=h=h^* \\ p=\hat{p}(h)}} < 0 \tag{6}$$

and is convergence stable if:

$$\left.\frac{\partial^2 \widehat{w}_H}{\partial h_m^2}\right|_{\substack{h_m=h=h^* \\ p=\hat{p}(h^*)}} + \left.\frac{\partial^2 \widehat{w}_H}{\partial h_m \partial h}\right|_{\substack{h_m=h=h^* \\ p=\hat{p}(h^*)}} < 0 \tag{7}$$

Equation (7) can be re-written in terms of the original host invasion fitness, w_H, as follows (for derivation see *Supplementary Materials*):

$$\frac{\partial^2 w_H}{\partial h_m^2} + \frac{\partial^2 w_H}{\partial h_m \partial h} + \frac{\partial^2 w_H}{\partial h_m \partial p}\frac{d\hat{p}}{dh} < 0 \tag{8}$$

where all terms are evaluated at $h_m = h = h^*$ and $p = p^*$.

This inequality may be interpreted geometrically in terms of a phase plane (see Fig. 1). The sum of the first two terms, $\frac{\partial^2 w_H}{\partial h_m^2} + \frac{\partial^2 w_H}{\partial h_m \partial h}$, represents the rate of change of the host component of the fitness gradient arrows as we move horizontally through the co-singular strategy. The term $\frac{\partial^2 w_H}{\partial h_m \partial p}$ represents the rate of change of the host component of the arrows as we move vertically through the co-singular strategy. The term $\frac{d\hat{p}}{dh}$ represents the gradient of the parasite nullcline at the co-singular strategy. Therefore, if the fitness gradient arrows point to the right on the left of the co-singular strategy and point to the left on the right of the co-singular strategy then a negative slope of the parasite nullcline promotes convergence stability (and vice versa).

Note that if (h^*, p^*) is a co-CSS (or is a boundary point that behaves like a co-CSS) in the classical adaptive dynamics framework, then it is also a co-CSS using the above separation of host and parasite evolutionary timescales. This is because strong convergence stability implies that all coevolutionary trajectories close to (h^*, p^*) converge to the co-singular point (note that equation (8) is a consequence of equations (2) for strong convergence stability whenever the parasite is also evolutionarily stable; see *Supplementary Materials*). The reverse implication does not always hold, however; just because coevolutionary trajectories where the parasite has a much faster rate of evolutionary change than the host converge to a particular point, it does not mean that all other trajectories will.

To illustrate the effects of separating evolutionary timescales, consider the phase planes in Fig. 1, where the co-singular point is found at the intersection of the nullclines for the host (black) and parasite (grey) fitness gradients. If the parasite evolves much faster than the host (red), then the coevolutionary trajectory rapidly moves to (or directly away from) the parasite nullcline and then follows the nullcline (or an edge of the phase plane). Convergence stability is determined by whether the trajectories move towards (Fig. 1A) or away from (Fig. 1B) the parasite nullcline, and then (if they do converge to the nullcline) whether they move along the parasite nullcline towards or away from the co-singular strategy.

However, even if all trajectories converge to the co-singular strategy when the parasite evolves much faster than the host, all trajectories may evolve away from the co-singular strategy (or cycle and therefore never approach it) when the rates of evolutionary change in both species are comparable (Fig. 1C,D; see also *Example 1* below). It is also possible for a co-

220 singular strategy to be an attractor of any mutational path with comparable rates of
221 evolutionary change but not of any mutational path where the parasite evolves much faster
222 than the host (such a co-singular strategy is not strong convergence stable, because it is not
223 an attractor of all mutational paths). This can lead to a case where the parasite trait is initially
224 convergence stable, but as the host trait subsequently evolves the trajectory moves to a
225 region where the parasite is not convergence stable. This can generate stable cycles in cases
226 where cycling is not seen for comparable rates of evolutionary change (Fig. 1E). A co-singular
227 strategy may also be convergence unstable for all mutational paths, but the relative rates of
228 evolutionary change may determine, for instance, whether both traits increase indefinitely or
229 whether one increases while the other falls (Fig. 1F).
230
231 What can we say in general about the nature of the phase plane for systems with disparate
232 and similar rates of evolutionary change, and the resulting coevolutionary trajectories?
233 Intuitively, when the parasite nullcline is an attractor and has a relatively shallow gradient
234 near a co-singular point, a relatively small change in the host phenotype does not lead to a
235 sudden, large change in the parasite phenotype. Coevolutionary trajectories therefore
236 gradually move along the parasite nullcline when the latter species evolves much faster,
237 converging to the same co-CSS as in classical adaptive dynamics (Fig. 1A). In contrast, when
238 the parasite nullcline has a relatively steep gradient near a co-singular point, a relatively small
239 change in the host phenotype leads to a sudden large shift in the parasite phenotype,
240 potentially leading to a difference in the long-term dynamics (Fig. 1C-E). Examining the
241 gradient and convergence stability of the parasite nullcline will therefore give a strong
242 indication as to whether the long-term dynamics of the system with disparate rates of
243 evolutionary change generalise to when rates of evolutionary change are more comparable.

244

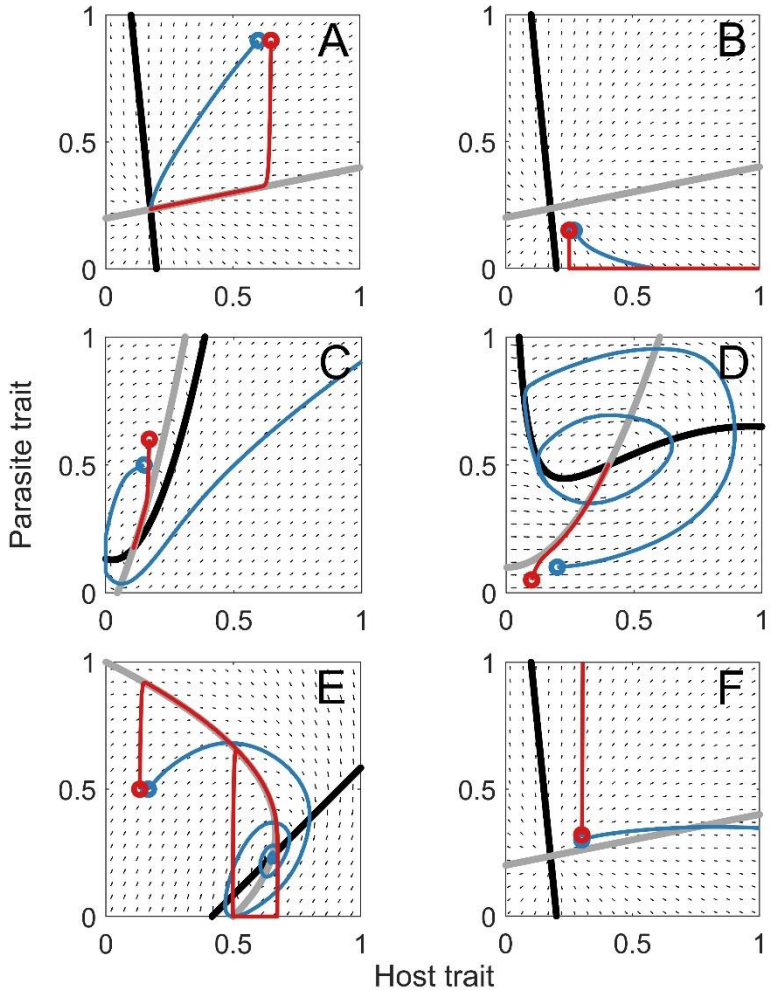

Fig. 1: Phase planes showing coevolutionary trajectories when the two species have comparable rates of evolutionary change (blue) and when the parasite evolves much faster than the host (red). In (A) and (B) the long-term outcome does not depend on the relative rates of evolutionary change, with both trajectories either converging to (A) or diverging from (B) the co-singular strategy. In (C) and (D) the traits converge to the co-singular strategy when the parasite evolves much faster than the host, but when the two species have comparable rates of evolutionary change, the traits may increase indefinitely (C) or cycle (D). In (E) both traits converge when the species evolve at comparable rates but cycle when the parasite evolves much faster than the host. In (F) both trajectories evolve away from the co-singular strategy, but towards different evolutionary endpoints. The host nullcline is shown in black and the parasite nullcline in grey. Circles mark the initial values of the evolving traits for the

given trajectories. Note that phase planes were generated manually to demonstrate a range of possible outcomes.

SCENARIO 2: POLYMORPHIC PARASITE POPULATION

If the singular strategy $\tilde{p}(h)$ is convergence stable (equation 5) but not evolutionarily stable (equation 4), then the parasite will branch into two traits (note that since we are essentially dealing with single trait evolution due to the separation of host and parasite timescales, mutual invasibility is implied (Geritz et al., 1998)). As a branching point is not an evolutionary endpoint, we must determine what eventually happens to the two parasite traits before we can consider the fate of a host mutation. We must therefore form a three species system with one host and two parasite species and modify the parasite invasion fitness to account for the two resident phenotypes, p_1 and p_2: $w_P^i(p_m^i, h, p_1, p_2)$. At this point, the analysis proceeds as in the monomorphic scenario to determine if there is a pair of co-singular strategies for the parasite $(\tilde{p}_1(h),\ \tilde{p}_2(h))$, given the current host trait value. If this point exists and is evolutionarily stable, then the invasion fitness of a rare host mutant is given by $\widehat{w}_H(h_m, h, \tilde{p}_1(h), \tilde{p}_2(h))$ and the analysis follows the same logic as above. If the parasite branches again, then one must modify the parasite invasion fitness to account for three resident phenotypes, and so on.

EXAMPLES

EXAMPLE 1: DIFFERENCES IN CONVERGENCE STABILITY

We consider the model of host-parasite coevolution proposed by Best *et al.* (2010) (Best et al., 2010). Susceptible hosts (with density S) reproduce at an underlying rate, a, subject to density-dependent competition, q (infected hosts do not reproduce). Disease transmission is also density-dependent with transmission rate β. Hosts die naturally at a constant rate, b, but infected hosts (with density I) also experience disease-induced mortality, α. We assume that there is no recovery from infection for simplicity. The ecological dynamics are modelled using the following system:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = (a - qN)S - bS - \beta SI \tag{9a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta SI - (\alpha + b)I \tag{9b}$$

We assume that the hosts and parasites have evolvable traits h and p respectively, which influence their life-histories through the trade-off functions $a = a(h)$ and $\beta = \beta(h, p)$ (as in (Best et al., 2010)). We consider the following functional forms for the trade-offs (for simplicity of calculations, these are different functional forms to the trade-offs used by Best *et al.* (2010) but have similar shapes and properties):

$$a(h) = a_0 + (a_1 - a_0)\frac{h - h_1}{h_0 - h_1} + \varepsilon(h - h_1)^2 \tag{10a}$$

$$\beta(h, p) = \frac{1}{4}\beta_0(p)(p - h + 4) \tag{10b}$$

$$\beta_0(p) = \beta_{0\min} + (\beta_{0\max} - \beta_{0\min})\frac{p - p_1}{p_0 - p_1} \tag{10c}$$

We assume that $h_0 \leq h \leq h_1$ and $p_0 \leq p \leq p_1$ (where $h_0 = p_0 = 0$ and $h_1, p_1 \leq 4$ to ensure that $\beta \geq 0$). We can see that the transmission rate of the parasite depends on the difference between the host and parasite traits ($p - h$) and so these traits can be interpreted as host

290 resistance to infection (which comes at a cost to host reproduction, a) and parasite infectivity
291 (which increases baseline transmissibility, β_0). We let ϕ represent the relative mutation rate
292 of the parasite trait (the parasite mutates ϕ times faster than the host).
293
294 Analytical calculations (given in the *Supplementary Materials*) show that, at any co-singular
295 strategy, the parasite is always evolutionarily stable, whereas the host may be evolutionarily
296 stable or unstable, depending on parameter values (hence branching may occur in the host
297 trait). The parasite is always convergence stable when evolving quickly relative to the host,
298 no matter the value of the host trait, and the host may also be convergence stable (depending
299 on parameter values). Strong convergence stability of the co-singular strategy is not
300 guaranteed.
301
302 These conditions mean that we can find parameter values (see Table S1) for which the co-
303 singular strategy is not strong convergence stable (and moreover the traits do not converge
304 when the rates of evolutionary change in the host and parasite are comparable), but where
305 both host and parasite traits are convergence stable when the parasite is evolving quickly
306 relative to the host (Fig. 2). In this particular case, the host and parasite traits converge to a
307 branching point when the parasite evolves much faster than the host (Fig. 2A,B). When the
308 host and parasite have comparable rates of evolutionary change, however, their traits do not
309 converge to their co-singular strategy and instead both tend to zero (Fig. 2C,D).
310
311 This example demonstrates that considering only the case of comparable rates of
312 evolutionary change, or considering sufficient (but not necessary) conditions like strong
313 convergence stability, may miss key predictions. In this case, both methods would conclude

that the co-singular strategy is not convergence stable, even though coevolutionary trajectories do converge whenever the parasite evolves sufficiently faster than the host. Therefore, if there is reason to believe that the parasite should evolve much faster than the host, separating the evolutionary timescales of the two species provides a more realistic prediction.

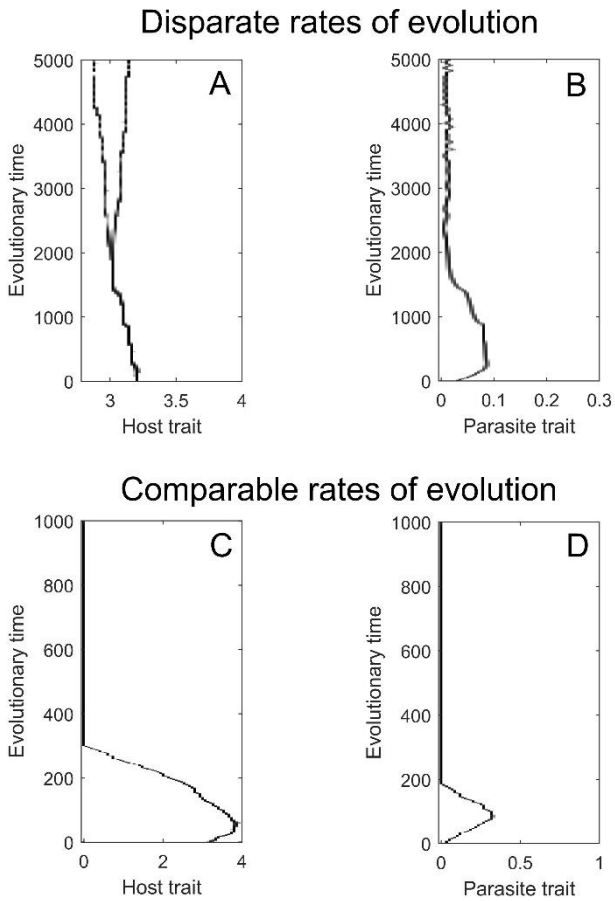

Fig. 2: Simulations showing the case where trajectories converge to the co-singular strategy when the parasite evolves much faster than the host (A & B; $\phi = 100$) but where the trajectories do not converge to the co-singular strategy when the host and parasite have comparable rates of evolutionary change (and hence the co-singular strategy is not strong convergence stable; C & D; $\phi = 1$). Parameters used are as in Table S1.

EXAMPLE 2: DIFFERENCES IN BRANCHING

Svennungsen & Kisdi (2009) consider the evolution of parasite virulence (disease-induced mortality, α) subject to a trade-off with transmissibility, $\beta(\alpha)$ (Svennungsen and Kisdi, 2009). Their model assumes that all hosts reproduce at a constant rate, b, and experience both density-independent and density-dependent intrinsic mortality, given by the parameters A and B, respectively. Disease transmission is density-dependent and infected hosts experience disease-induced mortality. These ecological dynamics are described by the following system:

$$\frac{\mathrm{d}S}{\mathrm{d}t} = bN - \beta(\alpha)SI - (A + BN)S \tag{11a}$$

$$\frac{\mathrm{d}I}{\mathrm{d}t} = \beta(\alpha)SI - (A + BN)I - \alpha I \tag{11b}$$

where N is the total host population density and the trade-off function is given by:

$$\beta(\alpha) = \frac{c\alpha}{a + \alpha}\left(1 - Ke^{-\frac{(\alpha-\bar{\alpha})^2}{\sigma^2}}\right) \tag{12}$$

This model has been shown to exhibit branching in virulence for a variety of parameter values (Svennungsen and Kisdi, 2009).

We can extend this model to consider coevolution with host resistance, r, subject to a trade-off with reproduction, b. To do this, we introduce the following functions:

$$c(r) = c_0(1 - r) \tag{13a}$$

$$b(r) = b_0\left(1 - \frac{c_1^b\left(1 - e^{c_2^b r}\right)}{1 - e^{c_2^b}}\right) \tag{13b}$$

with $c = c(r)$ in equation (12) corresponding to the level of host susceptibility and $b = b(r)$ in equation (11a) corresponding to the reproduction cost associated with resistance. We let

ϕ represent the relative mutation rate of the parasite trait (the parasite mutates ϕ times faster than the host).

The resistance trait, r, varies between zero (no resistance) and one (full resistance). When $r = 0$, we regain the original system with $b = b_0$ and $c = c_0$. As host resistance increases, the transmission rate between hosts, β, falls until complete resistance is reached (when $r = 1$, no transmission occurs). As resistance increases, host reproduction also falls (reaching a minimum level $b = b_0\left(1 - c_1^b\right)$ when $r = 1$). A summary of model parameters and variables is given in Table S2.

If host resistance is initially low enough and evolves sufficiently slowly relative to the parasite, then we know that parasite virulence can branch into two distinct phenotypes (Svennungsen and Kisdi, 2009). However, if the host and parasite have comparable rates of evolutionary change then branching does not necessarily occur for the same parameter values (Fig. 3). Even though the conditions for evolutionary stability of a co-singular strategy are the same for both the traditional adaptive dynamics framework (equation 1) and our new separation of evolutionary timescales method (equations 4 and 6), the incidence of branching does not need to be the same for all rates of evolutionary change. This is because it is possible for the only co-singular strategy to be a co-CSS (and hence when rates evolutionary change are comparable both species will evolve towards it and not branch) but for some points along the parasite nullcline far from the co-CSS to be evolutionarily unstable (and hence when the parasite evolves sufficiently fast, it may branch before the host has mutated). Whether the rates of evolution are disparate or comparable can also have a significant quantitative effect on the evolutionary equilibrium of the traits (e.g. Fig. 3A,C).

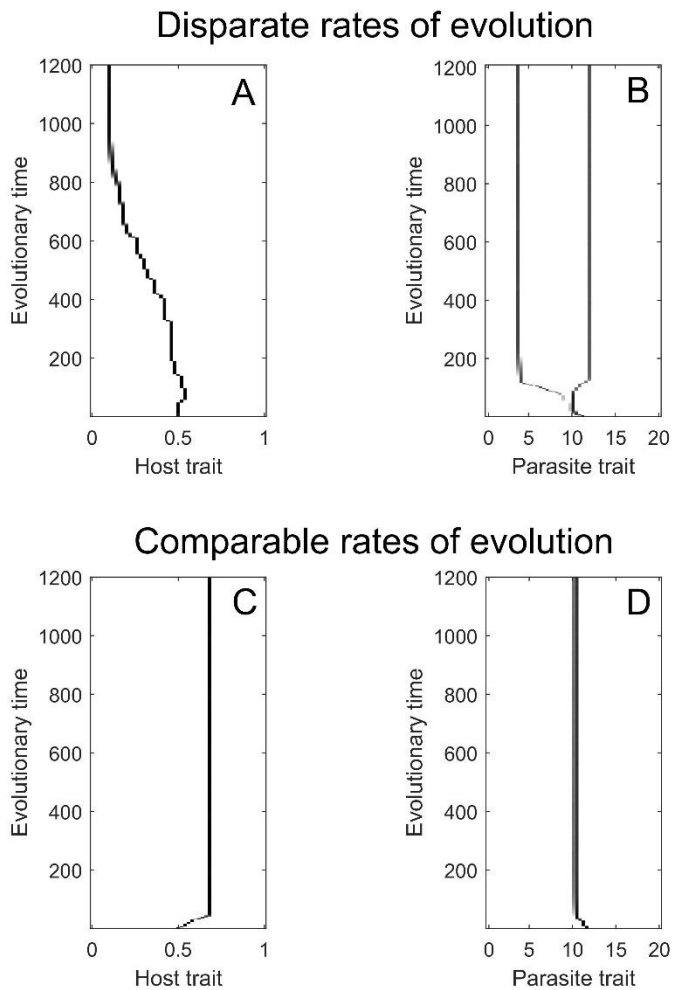

Fig. 3: Simulations showing the case where branching occurs when the parasite evolves much faster than the host (A & B; $\phi = 20$) but where the co-singular strategy is continuously stable (a co-CSS) when the host and parasite have comparable rates of evolutionary change (C & D; $\phi = 1$). Parameters used are as in Table S2.

Discussion

In many coevolving systems, especially those that involve more than one trophic level, evolution may proceed at very different rates within each species (Moran et al., 1995). This has important implications from a theoretical perspective, because coevolutionary convergence stability in adaptive dynamics depends on the relative rates of evolutionary change in the coevolving species (Dieckmann and Law, 1996; Marrow et al., 1996; Matessi and Pasquale, 1996). In this paper, we have shown how modelling the coevolution of two species on separate evolutionary timescales can greatly simplify model analysis and provide results which are more closely tailored to systems where species have contrasting rates of evolutionary change.

The relative rates of evolutionary change of two coevolving species can have a significant impact on coevolutionary outcomes (Dieckmann and Law, 1996; Marrow et al., 1996; Matessi and Pasquale, 1996). While some studies do consider the effect of varying relative rates of evolutionary change on coevolutionary dynamics (Best et al., 2010), many do not. Instead, models that use the adaptive dynamics framework typically either assume arbitrary rates of evolutionary change (e.g., (Best et al., 2008; Law et al., 2001; Rafaluk-Mohr et al., 2018)) or restrict analysis to cases where there is strong convergence stability (i.e., convergence stability holds for all rates of evolutionary change) (Best et al., 2009). Comparable rates of evolutionary change may be a good approximation for some biological systems (Nair et al., 2019; Naureen et al., 2020; Pollock et al., 2021), but in cases where species have very different evolutionary timescales (as is often true in host-microbe relationships), if similar rates are used in modelling then theoretical results may represent a significant departure from the real dynamics of natural populations.

Our approach considers the limit of rapid evolution in one species where it reaches an evolutionary endpoint (if one exists) before a mutation arises in the other species. This method was first used to model the coevolution of animal sociality and parasite virulence (Ashby and Farine, 2022), but here we have generalised the method and provided greater analytical details (e.g., conditions for convergence stability). Naturally, this method will provide a better approximation to biological systems which have greater differences between the rates of evolutionary change of the two species. Furthermore, the approximation is likely to generalise to comparable rates of evolutionary change when the nullcline for the fast evolving species has a relatively shallow gradient and is convergence stable.

If rates of evolutionary change are unknown for a given system, then one can only derive necessary or sufficient conditions for convergence stability or branching (Kisdi, 2006; Leimar, 2009). For instance, strong convergence stability is useful for proving that all coevolutionary trajectories tend to a particular point in trait space, but many of these trajectories will typically be unrealistic (e.g., parasites evolving much slower than their hosts). It is generally not important to know whether a particular result holds for all rates of evolutionary change, only whether it will hold for the typical rates of evolutionary change of the species in question (or the most likely rates of evolutionary change if they are unknown). In cases where one species is likely to evolve much faster than the other (e.g., host-parasite systems), separating their evolutionary timescales not only simplifies the analysis but may provide more realistic results by approximating the rapid evolution of one species.

There are two key advantages of our separation of evolutionary timescales method. First, our approximation gives a more straightforward definition of convergence stability when one species is known to evolve much faster than the other, rather than one which relies on relative rates of evolutionary change. Second, it is less computationally expensive because we are effectively only considering a one-dimensional manifold within a two-dimensional trait space. Rather than having to calculate the fitness gradient for every possible pair of traits, we only need to find them along the nullcline of the faster-evolving species. Together, these advantages mean that our method greatly simplifies and speeds up the analysis of coevolutionary models. Even if one is generally interested in a wide range of rates of evolutionary change, our method offers an efficient means of testing what happens when differences in these rates are large. Furthermore, the methods proposed herein could be readily extended to consider the coevolution of multiple traits in each species or additional separations of timescales across trophic levels (e.g., hosts, parasites and hyperparasites (Wood and Ashby, 2023)).

However, this method is clearly not appropriate for all coevolving species. We have shown that, in some cases, separating evolutionary timescales produces qualitatively and quantitatively different evolutionary outcomes to when species have comparable rates of evolutionary change. As such, this method is more suitable than others for modelling systems where one species evolves much faster than the other, but is not suitable for modelling systems in which the species evolve on similar timescales (e.g., in microbial communities, such as bacteria-phage coevolution). Still, our method offers a relatively straightforward test for determining whether results which assume comparable (or arbitrary) rates of evolutionary change still apply when one species evolves much faster than the other, and so will be

especially beneficial in scenarios restricted to plants/animals coevolving with microorganisms (e.g., parasite-mediated sexual selection/conflict (Ashby, 2020; Ashby and Boots, 2015; Hamilton and Zuk, 1982; Pirrie et al., 2022; Wardlaw and Agrawal, 2019)).

Overall, it is important to consider relative rates of evolutionary change when modelling the coevolution of two species. If rates of evolutionary change are likely to be similar, then it is important that the analysis is not over-simplified and the approximation presented herein may not be appropriate. However, if one species is known (or is likely) to evolve much faster than the other, then our method can greatly simplify the analysis and ensure more realistic predictions.

DATA AVAILABILITY

Source code is available in the *Supplementary Materials* and at: https://github.com/ecoevotheory/Buckingham_and_Ashby_2023c.

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464 **REFERENCES**

465 Ashby, B., 2020. Antagonistic coevolution between hosts and sexually transmitted infections.
466 Evolution (N Y) 74, 43–56. https://doi.org/10.1111/evo.13883

467 Ashby, B., Boots, M., 2015. The coevolution of parasite virulence and host mating strategies.
468 PNAS 112, 13290–13295.

469 Ashby, B., Farine, D.R., 2022. Social information use shapes the coevolution of sociality and
470 virulence. Evolution (N Y) 76, 1153–1169. https://doi.org/10.1101/2020.10.02.323451

471 Ashby, B., Iritani, R., Best, A., White, A., Boots, M., 2019. Understanding the role of eco-
472 evolutionary feedbacks in host-parasite coevolution. J Theor Biol 464, 115–125.
473 https://doi.org/10.1016/j.jtbi.2018.12.031

474 Bar-On, Y.M., Flamholz, A., Phillips, R., Milo, R., 2020. Sars-cov-2 (Covid-19) by the numbers.
475 Elife 9. https://doi.org/10.7554/eLife.57309

476 Best, A., Ashby, B., 2023. How do fluctuating ecological dynamics impact the evolution of
477 hosts and parasites? Philosophical Transactions of the Royal Society B 378.
478 https://doi.org/10.1098/rstb.2022.0006

479 Best, A., White, A., Boots, M., 2009. The implications of coevolutionary dynamics to host-
480 parasite interactions. American Naturalist 173, 779–791.
481 https://doi.org/10.1086/598494

482 Best, A., White, A., Boots, M., 2008. Maintenance of host variation in tolerance to pathogens
483 and parasites. PNAS 105, 20786–20791.

484 Best, A., White, A., Kisdi, É., Antonovics, J., Brockhurst, M.A., Boots, M., 2010. The evolution
485 of host-parasite range. American Naturalist 176, 63–71. https://doi.org/10.1086/653002

Bliven, K.A., Maurelli, A.T., 2016. Evolution of bacterial pathogens within the human host. Microbiol Spectr 4. https://doi.org/10.1128/microbiolspec.vmbf-0017-2015

Buckingham, L.J., Ashby, B., 2022. Coevolutionary theory of hosts and parasites. J Evol Biol 35, 205–224. https://doi.org/10.1111/jeb.13981

Day, T., Gandon, S., 2007. Applying population-genetic models in theoretical evolutionary epidemiology. Ecol Lett 10, 876–888. https://doi.org/10.1111/j.1461-0248.2007.01091.x

Dieckmann, U., Law, R., 1996. The dynamical theory of coevolution: a derivation from stochastic ecological processes. J Math Biol 34, 579–612.

Drew, G.C., Stevens, E.J., King, K.C., 2021. Microbial evolution and transitions along the parasite–mutualist continuum. Nat Rev Microbiol 19, 623–638. https://doi.org/10.1038/s41579-021-00550-7

Edmunds, G.F., Alstad, D.N., 1978. Coevolution in insect herbivores and conifers. Science (1979) 199.

Ehrlich, P.R., Raven, P.H., 1964. Butterflies and plants: A study in coevolution. Evolution (N Y) 18, 586–608.

Elena, S.F., Agudelo-Romero, P., Carrasco, P., Codoñer, F.M., Martín, S., Torres-Barceló, C., Sanjuán, R., 2008. Experimental evolution of plant RNA viruses. Heredity (Edinb) 100, 478–483. https://doi.org/10.1038/sj.hdy.6801088

Feeney, W.E., Welbergen, J.A., Langmore, N.E., 2014. Advances in the study of coevolution between avian brood parasites and their hosts. Annu Rev Ecol Evol Syst 45, 227–246. https://doi.org/10.1146/annurev-ecolsys-120213-091603

Ferriere, R., Fox, G.A., 1995. Chaos and evolution. Trends Ecol Evol 10, 480–485.

Ferriere, R., Gatto, M., 1995. Lyapunov exponents and the mathematics of invasion in oscillatory or chaotic populations. Theor Popul Biol 48, 126–171.

Flor, H.H., 1956. The complementary genic systems in flax and flax rust. Adv Genet 8, 29–54.

Futuyma, D.J., Agrawal, A.A., 2009. Macroevolution and the biological diversity of plants and herbivores. PNAS 106, 18054–18061.

Geritz, S.A.H., Kisdi, É., Meszéna, G., Metz, J.A.J., 1998. Evolutionarily singular strategies and the adaptive growth and branching of the evolutionary tree. Evol Ecol 12, 35–57.

Geritz, S.A.H., Kisdi, É., Yan, P., 2007. Evolutionary branching and long-term coexistence of cycling predators: Critical function analysis. Theor Popul Biol 71, 424–435. https://doi.org/10.1016/j.tpb.2007.03.006

Hamilton, W., Zuk, M., 1982. Heritable true fitness & bright birds: a role for parasites? Science (1979) 218, 384–387.

Hamilton, W.D., Axelrod, R., Tanese, R., 1990. Sexual reproduction as an adaptation to resist parasites. Proc. Natl. Acad. Sci. USA 87, 3566–3573.

Heiling, A.M., Herberstein, M.E., 2004. Predator-prey coevolution: Australian native bees avoid their spider predators. Proceedings of the Royal Society B 271, S196–S198. https://doi.org/10.1098/rsbl.2003.0138

Janzen, D.H., 1966. Coevolution of mutualism between ants and acacias in Central America. International Journal of Organic Evolution 20, 249–275.

Jarman, S.N., 2001. The evolutionary history of krill inferred from nuclear large subunit rDNA sequence analysis. Biological Journal of the Linnean Society 73, 199–212. https://doi.org/10.1006/bjls.2001.0538

531 Johnson, S.D., Anderson, B., 2010. Coevolution between food-rewarding flowers and their
532 pollinators. Evolution: Education and Outreach 3, 32–39.
533 https://doi.org/10.1007/s12052-009-0192-6
534 Karban, R., 1989. Fine-scale adaptation of herbivorous thrips to individual host plants. Nature
535 340, 60–61.
536 Kisdi, É., 2006. Trade-off geometries and the adaptive dynamics of two co-evolving species.
537 Evol Ecol Res 8, 959–973.
538 Klausmeier, C.A., 2008. Floquet theory: A useful tool for understanding nonequilibrium
539 dynamics. Theor Ecol 1, 153–161. https://doi.org/10.1007/s12080-008-0016-2
540 Law, R., Bronstein, J.L., Ferrière, R., 2001. On mutualists and exploiters: Plant-insect
541 coevolution in pollinating seed-parasite systems. J Theor Biol 212, 373–389.
542 https://doi.org/10.1006/jtbi.2001.2383
543 Leger, E.A., Espeland, E.K., 2010. Coevolution between native and invasive plant competitors:
544 Implications for invasive species management. Evol Appl 3, 169–178.
545 https://doi.org/10.1111/j.1752-4571.2009.00105.x
546 Leimar, O., 2009. Multidimensional convergence stability. Evol Ecol Res 11, 191–208.
547 Limborg, M.T., Heeb, P., 2018. Coevolution of hosts and their microbiome. Genes (Basel) 9.
548 https://doi.org/10.3390/genes9110549
549 Marrow, P., Dieckmann, U., Law, R., 1996. Evolutionary dynamics of predator-prey systems:
550 an ecological perspective. J Math Biol 34, 556–578.
551 Marshall, I.D., Fenner, F., 1960. Studies in the epidemiology of infectious myxomatosis of
552 rabbits: VII. The virulence of strains of myxoma virus recovered from Australian wild
553 rabbits between 1951 and 1959. Journal of Hygiene 58, 485–488.

554 Marshall, I.D., Fenner, F., 1958. Studies in the epidemiology of infectious myxomatosis of
555 rabbits: V. Changes in the innate resistance of Australian wild rabbits exposed to
556 myxomatosis. Journal of Hygiene 56, 288–302.
557 Matessi, C., Pasquale, C. Di, 1996. Long-term evolution of multilocus traits. J Math Biol 34,
558 613–653.
559 Meredith, R.W., Gatesy, J., Emerling, C.A., York, V.M., Springer, M.S., 2013. Rod
560 monochromacy and the coevolution of Cetacean retinal opsins. PLoS Genet 9.
561 https://doi.org/10.1371/journal.pgen.1003432
562 Metz, J.A.J., Geritz, S.A.H., Meszéna, G., Jacobs, F.J.A., Van Heerwaarden, J.S., 1995. Adaptive
563 dynamics: a geometrical study of the consequences of nearly faithful reproduction. IIASA
564 Working Papers.
565 Moran, N.A., Yon Dohlen, C.D., Baumann, P., 1995. Faster evolutionary rates in endosymbiotic
566 bacteria than in cospeciating insect hosts. J Mol Evol 41, 727–731.
567 Morran, L.T., Schmidt, O.G., Gelarden, I.A., Parrish, R.C., Lively, C.M., 2011. Running with the
568 Red Queen: Host-parasite coevolution selects for biparental sex. Science (1979) 333,
569 216–218. https://doi.org/10.1126/science.1206360
570 Nair, R.R., Vasse, M., Wielgoss, S., Sun, L., Yu, Y.T.N., Velicer, G.J., 2019. Bacterial predator-
571 prey coevolution accelerates genome evolution and selects on virulence-associated prey
572 defences. Nat Commun 10. https://doi.org/10.1038/s41467-019-12140-6
573 Naureen, Z., Dautaj, A., Anpilogov, K., Camilleri, G., Dhuli, K., Tanzi, B., Maltese, P.E., Cristofoli,
574 F., Antoni, L. De, Beccari, T., Dundar, M., Bertelli, M., 2020. Bacteriophages presence in
575 nature and their role in the natural selection of bacterial populations. Acta Biomedica
576 91, 1–13. https://doi.org/10.23750/abm.v91i13-S.10819

577 Nuismer, S.L., Ridenhour, B.J., Oswald, B.P., 2007. Antagonistic coevolution mediated by
578 phenotypic differences between quantitative traits. Evolution (N Y) 61, 1823–1834.
579 https://doi.org/10.1111/j.1558-5646.2007.00158.x
580 Paterson, S., Vogwill, T., Buckling, A., Benmayor, R., Spiers, A.J., Thomson, N.R., Quail, M.,
581 Smith, F., Walker, D., Libberton, B., Fenton, A., Hall, N., Brockhurst, M.A., 2010.
582 Antagonistic coevolution accelerates molecular evolution. Nature 464, 275–278.
583 https://doi.org/10.1038/nature08798
584 Pelletier, F., Garant, D., Hendry, A.P., 2009. Eco-evolutionary dynamics. Philosophical
585 Transactions of the Royal Society B 364, 1483–1489.
586 https://doi.org/10.1098/rstb.2009.0027
587 Pirrie, A., Chapman, H., Ashby, B., 2022. Parasite-mediated sexual selection: to mate or not
588 to mate?, in: Animal Behaviour and Parasitism. pp. 151–168.
589 Pollock, H.S., Hoover, J.P., Uy, F.M.K., Hauber, M.E., 2021. Brood parasites are a
590 heterogeneous and functionally distinct class of natural enemies. Trends Parasitol.
591 https://doi.org/10.1016/j.pt.2021.02.005
592 Pyenson, N.D., 2017. The ecological rise of whales chronicled by the fossil record. Current
593 Biology 27, R558–R564. https://doi.org/10.1016/j.cub.2017.05.001
594 Rafaluk-Mohr, C., Ashby, B., Dahan, D.A., King, K.C., 2018. Mutual fitness benefits arise during
595 coevolution in a nematode-defensive microbe model. Evol Lett 2, 246–256.
596 https://doi.org/10.1002/evl3.58
597 Sasaki, A., Dieckmann, U., 2011. Oligomorphic dynamics for analyzing the quantitative
598 genetics of adaptive speciation. J Math Biol 63, 601–635.
599 https://doi.org/10.1007/s00285-010-0380-6

600 Sender, R., Bar-On, Y.M., Gleizer, S., Bernshtein, B., Flamholz, A., Phillips, R., Milo, R., 2021.
601 The total number and mass of SARS-CoV-2 virions. PNAS 118.
602 https://doi.org/10.1073/pnas.2024815118/-/DCSupplemental
603 Svennungsen, T.O., Kisdi, É., 2009. Evolutionary branching of virulence in a single-infection
604 model. J Theor Biol 257, 408–418. https://doi.org/10.1016/j.jtbi.2008.11.014
605 Swierts, T., Vermeij, M.J.A., 2016. Competitive interactions between corals and turf algae
606 depend on coral colony form. PeerJ 2016. https://doi.org/10.7717/peerj.1984
607 Thompson, J.N., 2009. The coevolving web of life. American Naturalist 173, 125–140.
608 https://doi.org/10.1086/595752
609 Vermeij, G.J., Covich, A.P., 1978. Coevolution of freshwater gastropods and their predators.
610 Am Nat 112, 833–843.
611 Wardlaw, A.M., Agrawal, A.F., 2019. Sexual conflict and sexually transmitted infections (STIs):
612 coevolution of sexually antagonistic host traits with an STI. American Naturalist 193.
613 https://doi.org/10.5061/dryad.142p9j6
614 Wood, J., Ashby, B., 2023. Hyperparasitism and the evolution of parasite virulence. bioRxiv
615 preprint. https://doi.org/10.1101/2023.01.18.524570
616