

1 TRENDS BOX

- 2 • Host-parasite research has traditionally been conducted in a pairwise species
3 framework. Expanding investigations of host-parasite evolutionary interactions
4 into more complex communities, could illuminate patterns and processes
5 occurring in natural systems.
- 6 • There has been a recent surge of research which has sought to incorporate
7 increased biotic complexity in experimental designs, by including multiple
8 species of host, parasite or defensive mutualists.
- 9 • Such experiments have revealed the importance of biotic context in exploring
10 the nature of evolutionary interactions and where they fall on the parasite-
11 mutualist continuum.
- 12 • By combining evolutionary, ecological and genomic approaches, researchers
13 have begun to reveal the importance of feedbacks in communities and
14 understanding how these interactions are influenced by the addition of biotic
15 interactions.

Host and Parasite Evolution in a Tangled Bank

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Abstract

The majority of hosts and parasites exist in diverse communities wherein they interact with other species, spanning the parasite-mutualist continuum. These additional interactions have the potential to impose selection on hosts and parasites and influence the patterns and processes of their evolution. Yet, host-parasite interactions are almost exclusively studied in species pairs. A wave of new research has incorporated a multi-species community context, showing that additional ecological interactions can alter components of host and parasite fitness, as well as interaction specificity and virulence. We synthesize these findings to assess the effects of increased species diversity on the patterns and processes of host and parasite evolution. We argue that our understanding of host-parasite interactions would benefit from a richer biotic perspective.

A community context for host and parasite evolution

Darwin envisioned a 'Tangled Bank' [1], acknowledging that species exist and are under natural selection within a complex web of interactions. The majority of host and parasite species are part of diverse communities wherein additional interactions, across the parasite-mutualist continuum, are likely to profoundly influence their evolution. Although in the ecology literature host-parasite interactions are regularly studied in multi-species community contexts [2–6], until recently, evolutionary biology research has focussed almost exclusively on host and parasite species pairs [7].

In diverse ecological communities, the roles of different species cannot be limited by the definitions of host, parasite or mutualist. The species in a community form a network. Their interactions form links, the nature of which are context-dependent [8], and subject to feedbacks, even between species that interact indirectly (Figure 1, Key Figure). For example, some organisms can be traditionally considered parasites to their host, given the costs they confer, but can then act to protect hosts when a worse enemy attacks (e.g., cuckoos [9], defensive mutualists [10]). These shifts along the parasite-mutualist continuum highlight the importance of including a wider ecological context in experimental designs.

Ecological interactions between multiple species are well known to influence host and parasite life histories and fitness [2,4,7,11] differently from simple pairwise interactions. These effects, whether reducing or strengthening selection on hosts and parasites, are likely to shape the consequences of disease over time, influencing evolutionary trajectories and dynamics. Historically, it was often assumed that evolution was not fast enough to have a measurable effect on ecological dynamics and hence evolutionary consequences were not always considered in ecological studies [12]. This assumption is clearly not appropriate for many parasites which

change rapidly through antagonistic coevolution with their hosts [13]. In systems where the ecological and evolutionary processes can be observed on the same time scale, the feedbacks between the two processes can be measured, and these interlinked processes are referred to as eco-evolutionary dynamics [14]. Such feedbacks are important for understanding the spread of disease. They can be used to make predictions about how parasite life-history traits might change over time and how these changes might be expected to influence the growth rate of parasite populations.

Disentangling the effects of increasing community diversity on host-parasite evolutionary interactions can be challenging, especially when reliant on purely phenotypic measures. However, next-generation sequencing permits the full characterisation of evolutionary change by explicitly linking phenotype with genotype, and illuminating molecular mechanisms underlying evolutionary changes [15–17]. By combining changes in genotype with changes in the frequency of those genotypes, it is possible to test the predictions of coevolutionary models and determine the dynamics underlying coevolution [13,18].

New research has incorporated a larger community context to illuminate the effects of increased community complexity on the mechanisms, drivers, dynamics, and outcomes of host and parasite evolution (**Table 1**). Here, we review these studies, focusing particularly on those where interactions with additional species – hosts, enemies, or friends – have been considered. We then suggest future research directions that could build upon present findings and provide a community context for host-parasite evolutionary interactions.

Attack by antagonistic communities

In nature, some hosts are attacked by communities consistently dominated by a single parasite species acting as the primary source of selection [19,20]. Other infected host species can be under simultaneous attack from predators and competitors, with communities of antagonists varying in composition across time and space [21]. Multiple enemies can interact directly (e.g., competition between coinfecting parasites [15]) or indirectly via the host (e.g., parasites can increase host vulnerability to predation or reduce their competitive ability [22]), altering the evolutionary consequences across the entire community.

By sampling from natural populations over time, it is possible to make inferences about host-parasite coevolution in their full biotic context. This approach allows for time shift experiments [23], by freezing samples and comparing their infectivity or resistance with counterparts from other time points. The resultant matrix of infectivity and resistance over time allows the exploration of coevolutionary dynamics. However, as parasite diversity increases towards a tangled bank, the coevolutionary dynamics may become much less obvious or a dominant dynamic may conceal less obvious dynamics occurring simultaneously at a lower frequency [24].

Koskella and Parr [25,26] have sampled the microbiome of horse chestnut trees (*Aesculus hippocastanum*) alongside their parasitic bacteriophage communities over months, thus enabling the comparison of bacterial resistance between their contemporary phages and those from earlier months and across different trees. Some of the results [25] showed that from the phage's perspective, future bacteria are always more resistant. This pattern is consistent with arms race dynamics (ARD) which predict directional selection for increased resistance in hosts and increased infectivity in parasites [27]. Interestingly, the same study system has previously produced patterns more consistent with fluctuating selection dynamics (FSD) [26].

95 Under FSD, genotypes are under negative, frequency-dependent selection causing
96 genotype frequencies to oscillate through time and producing patterns of local
97 temporal adaptation [28]. The authors provide several logical explanations for the
98 different outcomes [25] such as the time window of the experiment being insufficient
99 to detect a strong signal of local adaptation. However, laboratory investigations have
100 shown that different parasites can display different coevolutionary dynamics with the
101 same host under the same conditions [29]. Such divergent evolutionary outcomes
102 could arise as a consequence of coevolution within a wider community context where
103 higher order ecological interactions or coevolution amongst parasites, as well as
104 between hosts and parasites, could drive trait evolution.

105 When evolution occurs rapidly, the diversity of a community can influence the relative
106 importance of ecological and evolutionary dynamics, especially in the face of multiple
107 enemies [30]. Theory predicts that if a single generalist phenotype evolves to provide
108 resistance to multiple enemies, the ecological dynamics of a multi-enemy community
109 may resemble a simple pairwise interaction [31]. Increasing parasite diversity may
110 allow such an outcome via diffuse coevolution, but only when there is genetic
111 correlation between parasite resistance mechanisms and when the coevolutionary
112 trajectories of the individual parasites are affected by the presence of others [32]. If
113 there is no genetic correlation between resistance mechanisms then only pairwise

114 coevolution can occur allowing for independent coadaptation [33]. The prevailing
115 mode of coevolution, whether diffuse or pairwise, has implications for biological
116 control, for example in phage therapy [34] where artificial communities of
117 bacteriophage are assembled to control bacterial infection [35]. If resistance to one
118 phage confers resistance to others [36] then some of the advantages of phage

119 communities over monocultures [37] could disappear. Such applications of biological
120 control should be considered within a coevolutionary framework [38].

121 Coevolutionary theory also has interesting implications for the maintenance of
122 parasite diversity. ARD predicts the existence of universally resistant or infective
123 hosts and parasites [39]. The presence of such a 'super' generalist could result in the
124 loss of diversity by disrupting the negative, frequency-dependent selection or kill the
125 winner [40], dynamics which drive ecological turnover (e.g. the relative frequencies of
126 host and parasite over time). In theory, this dynamic could facilitate the reduction of
127 an initially diverse community of enemies to a simple pairwise interaction as some
128 enemies dwindle towards extinction [41]. For diversity to be maintained, some
129 mitigating effect such as spatial structure [42] or fitness costs [43] must act to
130 interrupt the rise of super hosts or parasites.

131 In multi-species coinfections, parasites can interact either cooperatively [44] to the
132 detriment of their host or competitively to detriment of one another [15]. Although it is
133 unclear to what extent these coinfections alter patterns of host and parasite
134 evolution, experiments have shown that such interactions can have important
135 consequences for parasite ecological dynamics [45]. Exposing the three-spined

136 stickleback (*Gasterosteus aculeatus*) host to the tapeworm *Schistocephalus solidus*
137 affected the susceptibility of the host to superinfection by naturally occurring parasite
138 communities resident in the lake where the experiment was performed. Some
139 parasites were better able to infect hosts already infected by *S. solidus* whereas
140 others found already infected hosts to be more resistant. These results were then
141 confirmed by experimentation in a laboratory setting. The authors argue that further
142 investigations manipulating parasite diversity are required to understand how inter-
143 specific parasite interactions can shape parasite communities [46].

144 Combined selection by parasites and predators can alter the dynamics of host
145 evolution and modify host phenotypes pleiotropically [47]. There has been a recent
146 effort to develop a theoretical framework to explore such interactions [48–52]. These
147 models have made links between ecological and evolutionary processes. For
148 example, high predator density is predicted to select for lower virulence in pathogens
149 of the prey [48], and combined selection by predators and parasites can drive the
150 evolution of host diversity [51].

151 Whilst empirical evidence of the ecological effects of combined predation and
152 parasitism is well documented [53,54], experimental studies which also include an
153 evolutionary perspective are still relatively uncommon. Parasitism or predation of
154 *Pseudomonas aeruginosa* (an opportunistic human pathogen) by the bacteriophage
155 PNM or the protist *Tetrahymena thermophila* have been shown via experimental
156 evolution [55] to select for *P. aeruginosa* phenotypes that show reduced virulence in
157 wax moth larvae. Protist predation alone selects for reduced virulence relative to
158 phage parasitism alone and combined selection by both results in an intermediate
159 level of virulence between the two. Experiments have started to show the importance
160 that pleiotropy can have for hosts and parasites [56]. Detecting such effects has been

161 made easier through advances in genomics [57] and will be crucial as experiments
162 seek to elucidate the processes underlying coevolution with multiple parasites.

163 **Parasite evolution in host communities**

164 Multiple available hosts, as well as the presence of multiple parasites, can strongly
165 influence host-parasite evolutionary interactions. Host shifts in parasite evolutionary
166 history are common [45] and can be detected by comparing the phylogenies of
167 parasite and host [58,59]. Ninety-three percent of studies comparing host and

168 parasite phylogeny find evidence of a host shift [58] and in some phylogenetic groups
169 huge percentages of parasites infect multiple hosts (e.g. multi host RNA viruses
170 infecting primates, carnivores and ungulates) [60]. Ninety-six percent of viruses
171 infecting primates are able to infect multiple host species [60] and although host
172 shifts are generally predicted to occur among phylogenetically close host lineages
173 [60], switches to more distant host lineages do occur and are predicted to occur by
174 some models [61]. An inter-kingdom host switch has even been reported in the
175 human acne causing bacterium, *Propionibacterium acnes*, which has switched hosts
176 from humans to the grapevine plant [62]. Given the extent to which host shifts occur
177 in nature [58], a greater knowledge of their drivers and consequences is likely to be
178 critically important to understanding natural host-parasite evolutionary dynamics [59].

179 Models predict that the availability of multiple host species can influence the
180 trajectory of parasite evolution [60,61]. Empirical evidence supports this prediction
181 [63], for example leading to trade-offs where coevolution with a new host reduces
182 infectivity on the previous host [64]. The susceptibility of novel hosts is difficult to
183 predict [65]; however, novel hosts which are more closely related to the ancestral
184 host are often more susceptible [65,66].

185 For host shifts to occur, the parasite must possess the ability to infect a variety of
186 hosts [67], and certain infection genetics models are more likely to selected for this
187 property in parasites [68,69]. For example, the inverse matching allele (IMA) infection
188 model (where a parasite can only infect if it does not match a corresponding
189 recognition allele in the host [70]) is much more likely to lead to host shift than the
190 gene for gene (GFG) (which predicts the existence of a parasite genotype capable of
191 infecting all host genotypes [23]) or matching allele (MA) (where a parasite can only
192 infect when it does match a corresponding allele in the host [42]) models [68].

193 Furthermore, in a model specifically focussing on bacteria, exposure to multiple hosts
194 has been predicted to select for modification of the environment through cooperative
195 secretions, such as biofilms or virulence factors, in order to allow infection of multiple
196 hosts [71], a prediction supported by comparative phylogenetic data [71]. Together,
197 the predictions of these models indicate that the opportunity to switch hosts is likely
198 to influence host and parasite evolutionary trajectories.

199 Studies of natural systems have further shed light on the effects of host-shifts on
200 parasite evolution. In some natural systems, trade-offs in parasite evolution shapes
201 adaptation to new hosts [72,73]. The diversity of hosts available to a parasite can
202 further influence key evolutionarily relevant parasite traits. Transmission of the
203 trematode *Ribeiroia ondatrae* is negatively influenced by diversity of its amphibian
204 hosts, both in controlled laboratory experiment and outdoor mesocosms [75].

205 Furthermore, the evolutionary trajectory of the bacterium *Mycoplasma gallisepticum*
206 following a host switch from poultry to the North American house finch has been
207 shaped by trade-offs between transmission, virulence and recovery rates in the new
208 host, with increased virulence reducing the rate the host is able to clear the infection
209 [73]. Similarly, in the famous example of the release of the *myxoma* virus in

210 Australian rabbits, parasite evolution was shaped by virulence- transmission trade-
211 offs [72]. The myxoma virus was released in the 1950's as an attempt to control the
212 population size of European rabbits which had become an invasive species in
213 Australia. The virus was initially very virulent (99.8% mortality in infected rabbits), but
214 where less virulent strains of the virus emerged host rabbits lived longer thereby
215 increasing viral transmission. This selection for less virulent strains combined with
216 coevolution by the rabbit, led to the mortality caused by the myxoma virus reducing to
217 70-95% [74].

218 The effects of host shifts are yet to be thoroughly evaluated via experimental
219 evolution, with but a few exceptions to our knowledge. Experimentally adapting the
220 bacteriophage $\Phi X174$ on the novel host *Salmonella enterica* led to a trade-off where
221 infectivity in the traditional host *E. coli* was reduced [64]. More recently, experimental
222 evolution of the tobacco etch potyvirus (TEV) in varying plant hosts has
223 demonstrated that many phenotypic and genotypic changes are host specific [76,77].
224 In spite of this, strains of TEV showed parallel evolution in their infectivity of different
225 host species when evolving experimentally on either alternating host plant species or
226 on single host species, and there did not seem to be any costs of generalism [76].
227 More controlled experiments are needed, however, to make broader conclusions on
228 the influence of the availability of multiple hosts on parasite and host evolution.

229 Models and studies of natural systems indicate that the number of available host
230 species matters when predicting outcomes of host-parasite evolutionary interactions.

231 At present research into the effects of multiple potential host species on host-parasite
232 coevolution is lagging behind research investigating the effects of multiple infection in
233 a single host species or strain. Nevertheless, the few studies that have approached
234 the question to date have shown that the effects are likely to be significant [73,75,78].

235 Paired with the fact that host shifts are common in nature for some parasites

236 [59,60,58], there is a strong argument that the effects of multiple simultaneously

237 available host species warrants further experimental investigation.

238 **Mutualisms in the tangled bank.**

239 Hosts can harbour a diversity of organisms in addition to parasitic ones that can be

240 beneficial.

241 Among natural populations of animals [79–82], plants [83–85], and even humans
242 [86], are beneficial microbes that can protect their hosts against infection by parasites
243 [87]. Such ‘defensive mutualists’ can reduce parasite colonisation by competing
244 directly via toxin production or indirectly via resource extraction and host-mediated
245 processes [88]. It has also been shown that mildly parasitic microbes can cross the
246 parasite-mutualist continuum and rapidly evolve these host-protective traits [16].
247 Given their impact on host and parasite fitness, defensive mutualists have the
248 potential to strongly influence host-parasite evolutionary interactions [89–92]. For
249 example, it has been argued that, through host immune system effects, defensive
250 mutualists can either enhance or diminish the selective effects of a parasite [93],
251 which could in turn effectively alter patterns of host-based resistance [94] and
252 parasite virulence. Moreover, studies have shown that defensive mutualists can drive
253 variation in resistance and underlying host-parasite specificity [95,96]. Host-parasite
254 specificity is a fundamental assumption of coevolution [39], and if parasites adapt to
255 these genotype-specific microbes [95,97], then defensive mutualists have the
256 potential to mediate host-parasite coevolutionary interactions and even coevolve
257 themselves [98].

258 In a complex community, species interactions can be context-dependent. Shifts along
259 the parasitism-mutualism continuum in one pairwise interaction may drive similar
260 shifts in other interactions [99]. For example, if a third interacting species is purely
261 exploitative and parasitic, then it may destabilise a focal mutualism [92]. In a focal
262 pairwise public goods-based mutualism between *Escherichia coli* (secreting a carbon
263 source) and *Salmonella enterica* (secreting an amino acid), both species were
264 dependent on the secretions of the other for growth [99]. The frequency of a non-
265 secretor *S. enterica* genotype, a parasite, that did not contribute but nonetheless

exploited the focal mutualism was measured over time to test the effects of spatial structure on the evolution of cooperation [100]. A third species was then added to this system, *Methylobacterium extorquens*, modified such that it was dependent on the carbon from *E. coli* but itself secreted a source of nitrogen [101]. Therefore, here the interactions with *M. extorquens* transitioned from parasitic to mutualistic depending on the concentration of nitrogen provided in the growth media. Contrary to theoretical predictions [92,102], in this case adding a parasite (*M. extorquens* stealing carbon) increased selection for mutualism (*S. enterica* secretors) and adding a mutualist (*M. extorquens* providing nitrogen) decreased it [99]. This multi-species system serves to reinforce the importance of context for the nature of selection acting on mutualisms.

Concluding Remarks and Future Perspectives

The studies reviewed here clearly demonstrate that additional species strongly influence the patterns and processes of host-parasite evolutionary interactions. Considering the importance of more species in the community exponentially increases the number of possible interactions and the scope for eco-evolutionary feedbacks.

Additional species can also influence the evolutionary trajectory of host and parasite

283 traits including the degree co-adaptation [40,76]; and virulence evolution [37,93,103].
284 Depending on the between-parasite interactions in multiple infections, evolution can
285 lead to either an increase or decrease in overall virulence [37,103], an outcome of
286 infection which can also be profoundly affected by host shifts.[72,73]. Similarly, the
287 ability of defensive microbes to dampen the selective effects a parasite gives them
288 the propensity to influence parasite virulence evolution [93].

289 Recent work has demonstrated the importance of the wider ecological community in
290 influencing evolutionary outcomes and dynamics for host and parasite. Although in
291 the last few years additional players and genomics have been increasingly
292 incorporated into research on host-parasite interactions, there remains a huge scope
293 to explore the effects of additional players on host-parasite evolution and coevolution
294 (see Outstanding Questions). Critically, understanding how species diversity
295 influences host and parasite evolution will enhance our ability to predict and
296 understand the outcomes and dynamics of host-parasite evolutionary interactions in
297 nature. From the studies discussed herein, it is clear that the evolution of key traits
298 including host resistance and parasite infectivity cannot be understood in the context
299 of bipartite interactions alone in many systems.

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304 **Table 1. Selection experiments demonstrating effects of additional species interactions on host and/or parasite evolution**

Additional Player	Focal Host	Focal Enemy	Trait Measured		Result	Refs
			Host/prey	Other		
PARASITE						
Multiple phage	<i>Pseudomonas syringae</i>	Single phage	Resistance, cost of resistance		Hosts evolving with multiple parasites were no more resistant to allopatric parasites but paid a higher cost for their resistance	[104]
	<i>Pseudomonas aeruginosa</i>	Single phage	Resistance and breadth of resistance		Broadest resistance range evolved in response to parasite diversity.	[15]
PREDATOR						
Tetrahymena thermophila	<i>Serratia marcescens</i> or <i>Pseudomonas fluorescens</i>	Bacteriophage <i>Semad11</i> or <i>phi2</i>	Resistance		Adding predators reduced resistance to parasites.	[105]
	<i>Pseudomonas fluorescens</i>	Bacteriophage <i>phi2</i>	Resistance	Coevolutionary dynamics	Reduced signal of arms race dynamics. Reduced resistance overall	[106]

					due to subdivision in specialists	
	<i>P. aeruginosa</i>	Bacteriophage <i>PNM</i>	Resistance, Virulence		Phage + predator attenuated <i>P. aeruginosa</i> virulence less than phage alone. Greater phenotypic divergence.	[55]
COMPETITOR						
Aphis nerii	<i>Danaus plexippus</i> (on milkweed <i>Asclepias</i> spp.)	<i>Ophryocystis elektroscirrha</i>		Virulence, transmission	Addition of <i>A. nerii</i> increased <i>O. elektroscirrha</i> virulence and transmission.	[22]
HOST						

Alternating between <i>Nicotiana benthamiana</i> , <i>Datura stramonium</i> and <i>Capsicum annuum</i>	<i>Nicotiana tabacum</i>	Tobacco etch poty- virus		Genomics, fitness	Genomics revealed host specific mutations. Virus was fitter on sympatric hosts. No evidence of cost for generalists.	[76]
Distant hosts; <i>Brassica oleracea</i> var. <i>Bartolo</i> and <i>Phaseolus vulgaris</i> var. <i>Blanc Précoce</i>	Original hosts; <i>Solanum lycopersicum</i> , <i>S. melongena</i> var. <i>Zebrina</i> and <i>Geranium sanguineum</i> var. <i>Maverick</i> <i>Ecarlate</i>	<i>Ralstonia solanacearum</i>		Genomics, fitness	Parasite increased in (sympatric) fitness on all hosts but biggest increase in distant hosts. Parallel evolution in a single gene led to increased fitness in beans.	[77]
MUTUALIST						
<i>Hamiltonella defensa</i>	<i>Aphis fabae</i>	<i>Lysiphlebus fabarum</i>		Infectivity	Protected hosts selected for increased infectivity.	[97]

<i>Enterococcus faecalis</i>	<i>Caenorhabditis elegans</i>	<i>Staphylococcus aureus</i>		Mutualist-mediated protection	Defensive mutualist evolved increased protective ability.	[16]
<i>Wolbachia</i>	<i>Drosophila melanogaster</i>	<i>Drosophila C virus</i>	Resistance		Host resistance allele at lower frequency in populations with defensive mutualist.	[94]

Figure 1, Key Figure. The Context Dependence of a Focal Pairwise Host-Parasite Relationship. FOCAL RELATIONSHIP; 1 and 2) The focal relationship between a host and a parasite, parasite growth, is a function of host population size and acts to reduce host growth. Any feedback which increases growth of the focal parasite will decrease growth in the focal host and any feedback which increases host growth will increase parasite growth. ADDITIONAL PARASITE SPECIES; 3) an additional parasite may directly increase the growth of the focal parasite through synergistic means, perhaps a form of public goods cooperation. 4) Alternatively the new parasite may compete with the focal parasite for host resources and reduce its growth. COMPETITOR/PREDATOR; 5) a competitor or predator will decrease growth in the focal host which will feedback into reduced growth of the focal parasite. ADDITIONAL HOST SPECIES; 6) the additional host species may increase growth in the focal host if it provides some form of social immunity. 7) An additional host species may serve to fuel growth in the focal parasite population. DEFENSIVE MUTUALIST; 8) a defensive mutualist will reduce the growth of the focal parasite which will feedback into increase growth in the focal host.

References

- 1 Darwin, C. (1909) *The Origin of Species*, P. F. Collier & Son.
- 2 Hall, S.R. *et al.* (2007) Eating yourself sick: transmission of disease as a function of foraging ecology. *Ecol. Lett.* 10, 207–218
- 3 Rohr, J.R. *et al.* (2008) Parasites, info-disruption, and the ecology of fear. *Oecologia* 159, 447–454
- 4 Raveh, A. *et al.* (2011) Driven to distraction: detecting the hidden costs of flea

329 parasitism through foraging behaviour in gerbils. *Ecol. Lett.* 14, 47–51

330 5 Smith, L.A. *et al.* (2009) Livestock grazing behavior and inter- versus

331 intraspecific disease risk via the fecal–oral route. *Behav. Ecol.* 20, 426–432

- 332 6 Brambilla, A. *et al.* (2013) Don't spit in the soup: faecal avoidance in foraging
333 wild Alpine ibex, *Capra ibex*. *Anim. Behav.* 86, 153–158
- 334 7 Rigaud, T. *et al.* (2010) Parasite and host assemblages: embracing the reality
335 will improve our knowledge of parasite transmission and virulence. *Proc. R.*
336 *Soc. London B Biol. Sci.* 277, 3693–3702
- 337 8 Daskin, J.H. and Alford, R.A. (2012) Context-dependent symbioses and their
338 potential roles in wildlife diseases. *Proc. Biol. Sci.* 279, 1457–65
- 339 9 Canestrari, D. *et al.* (2014) From Parasitism to Mutualism: Unexpected
340 Interactions Between a Cuckoo and Its Host. *Science* 343, 1350–1352
- 341 10 Martinez, J. *et al.* (2014) Symbionts Commonly Provide Broad Spectrum
342 Resistance to Viruses in Insects: A Comparative Analysis of *Wolbachia* Strains.
343 *PLoS Pathog.* 10, 1–13
- 344 11 Turner, W.C. *et al.* (2014) Fatal attraction: vegetation responses to nutrient
345 inputs attract herbivores to infectious anthrax carcass sites. *Proc. R. Soc.*
346 *London B Biol. Sci.* 281, 20141785
- 347 12 Pelletier, F. *et al.* (2009) Eco-evolutionary dynamics. *Philos. Trans. R. Soc. B*

348

Biol. Sci. 364, 1483–1489

349

13

Brockhurst, M.A. *et al.* (2014) Running with the Red Queen: the role of biotic

350

conflicts in evolution. *Proc. R. Soc. B Biol. Sci.* 281, 20141382

351

14

Post, D.M. and Palkovacs, E.P. (2009) Eco-evolutionary feedbacks in

352

community and ecosystem ecology: interactions between the ecological theatre

353

and the evolutionary play. *Philos. Trans. R. Soc. B Biol. Sci.* 364, 1629–1640

354

15

Betts, A. *et al.* (2016) Parasite diversity drives rapid host dynamics and

355 evolution of resistance in a bacteria-phage system. *Evolution* DOI:

356 10.1111/evo.12909

357 16 King, K.C. *et al.* (2016) Rapid evolution of microbe-mediated protection against

358 pathogens in an animal host. *Rev.* DOI: 10.1038/ismej.2015.259

359 17 Paterson, S. *et al.* (2010) Antagonistic coevolution accelerates molecular

360 evolution. *Nature* 464, 275–8

361 18 Barrick, J.E. and Lenski, R.E. (2013) Genome dynamics during experimental

362 evolution. *Nat. Publ. Gr.* 14, 827–839

363 19 Lively, C.M. (1987) Evidence from a New Zealand snail for the maintenance of

364 sex by parasitism. *Nature* 328, 519–521

365 20 King, K.C. and Lively, C.M. (2009) Geographic variation in sterilizing parasite

366 species and the Red Queen. *Oikos* 118, 1416–1420

367 21 Thompson, J. (2005) *Geographic Mosaic of Coevolution*, The University of

368 Chicago Press.

369 22 de Roode, J.C. *et al.* (2011) Aphids indirectly increase virulence and

370 transmission potential of a monarch butterfly parasite by reducing defensive

371 chemistry of a shared food plant. *Ecol. Lett.* 14, 453–461

372 23 Gaba, S. and Ebert, D. (2009) Time-shift experiments as a tool to study

373 antagonistic coevolution. *Trends Ecol. Evol.* 24, 226–232

374 24 Rabajante, J.F. *et al.* (2016) Host-parasite Red Queen dynamics with phase-

375 locked rare genotypes. *Sci. Adv.* 2, 1–7

376 25 Koskella, B. and Parr, N. (2015) The evolution of bacterial resistance against

377 bacteriophages in the horse chestnut phyllosphere is general across both

378 space and time. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 370,

379 26 Koskella, B. (2014) Bacteria-Phage Interactions across Time and Space:

380 Merging Local Adaptation and Time-Shift Experiments to Understand Phage

381 Evolution. *Am. Nat.* 184 Suppl, S9–S21

382 27 Quigley, B.J.Z. *et al.* (2012) The mode of host-parasite interaction shapes

383 coevolutionary dynamics and the fate of host cooperation. *Proc. R. Soc. B Biol.*

384 *Sci.* 279, 3742–8

385 28 Gandon, S. *et al.* (2008) Host-parasite coevolution and patterns of adaptation

386 across time and space. *J. Evol. Biol.* 21, 1861–6

387 29 Betts, A. *et al.* (2014) Contrasted coevolutionary dynamics between a bacterial

388 pathogen and its bacteriophages. *Proc. Natl. Acad. Sci. U. S. A.* 111, 11109–

389 11114

390 30 Friman, V.-P. *et al.* (2015) Relative importance of evolutionary dynamics

391 depends on the composition of microbial predator–prey community. *ISME J.*

392 DOI: 10.1038/ismej.2015.217

393 31 Ellner, S.P. and Becks, L. (2011) Rapid prey evolution and the dynamics of

394 two-predator food webs. *Theor. Ecol.* 4, 133–152

395 32 Iwao, K. and Rausher, M. (1997) Evolution of plant resistance to multiple
396 herbivores: quantifying diffuse coevolution. *Am. Nat.* 149, 316–335

397 33 Hougén-Eitzman, D. and Rausher, M. (1994) Interactions between herbivorous
398 insects and plant-insect coevolution. *Am. Nat.* 143, 677–697

399 34 Reardon, S. (2014) Phage therapy gets revitalized. *Nature* 510, 15–16

400 35 Chan, B.K. *et al.* (2013) Phage cocktails and the future of phage therapy.

401 *Future Microbiol.* 8, 769–83

402 36 Betts, A. *et al.* (2013) Back to the future: evolving bacteriophages to increase
403 their effectiveness against the pathogen *Pseudomonas aeruginosa* PAO1.
404 *Evol. Appl.* 6, 1054–63

405 37 Schmerer, M. *et al.* (2014) Synergy as a rationale for phage therapy using
406 phage cocktails. *PeerJ* 2, e590

407 38 Torres-Barceló, C. and Hochberg, M.E. (2016) Evolutionary Rationale for
408 Phages as Complements of Antibiotics. *Trends Microbiol.* 24, 249–246

409 39 Agrawal, A. and Lively, C. (2002) Infection genetics: gene-for-gene versus
410 matching-alleles models and all points in between. *Evol. Ecol. Res.* 4, 79–90

411 40 Rodriguez-Brito, B. *et al.* (2010) Viral and microbial community dynamics in
412 four aquatic environments. *ISME J.* 4, 739–751

413 41 Rabajante, J.F. *et al.* (2015) Red Queen dynamics in multi-host and multi-
414 parasite interaction system. *Sci. Rep.* 5, 10004

415 42 Salathé, M. *et al.* (2008) The state of affairs in the kingdom of the Red Queen.
416 *Trends Ecol. Evol.* 23, 439–445

417 43 Hall, A.R. *et al.* (2011) Host-parasite coevolutionary arms races give way to
418 fluctuating selection. *Ecol. Lett.* 14, 635–42

419 44 Cézilly, F. *et al.* (2014) Cooperation and conflict in host manipulation:
420 Interactions among macro-parasites and micro-organisms. *Front. Microbiol.* 5,
421 1–1

422 45 Susi, H. *et al.* (2015) Co-infection alters population dynamics of infectious
423 disease. *Nat. Commun.* 6, 5975

424 46 Benesh, D.P. and Kalbe, M. (2016) Experimental parasite community ecology :
 425 intraspecific variation in a large tapeworm affects community assembly. *J.*
 426 *Anim. Ecol.* 85, 1004–1013

427 47 Zhang, J. *et al.* (2014) Coincidental Loss of Bacterial Virulence in Multi-Enemy
 428 Microbial Communities. *PLoS One* 9, e111871

429 48 Kisdi, E. *et al.* (2013) Evolution of pathogen virulence under selective
 430 predation: A construction method to find eco-evolutionary cycles. *J. Theor. Biol.*
 431 339, 140–150

432 49 Morozov, A.Y. and Adamson, M.W. (2011) Evolution of virulence driven by
 433 predator – prey interaction: Possible consequences for population dynamics. *J.*
 434 *Theor. Biol.* 276, 181–191

435 50 Bairagi, N. and Adak, D. (2016) Mathematical Biosciences Switching from
 436 simple to complex dynamics in a predator – prey – parasite model : An
 437 interplay between infection rate and incubation delay. *Math. Biosci.* 277, 1–14

438 51 Toor, J. and Best, A. (2016) Evolution of Host Defense against Multiple Enemy
 439 Populations. *Am. Nat.* 187,

440 52 Morozov, A. and Best, A. (2012) Predation on infected host promotes
441 evolutionary branching of virulence and pathogens ' biodiversity. *J. Theor. Biol.*
442 307, 29–36

443 53 Martini, X. *et al.* (2014) Plant pathogen-induced volatiles attract parasitoids to
444 increase parasitism of an insect vector. *Front. Ecol. Evol.* 2, 1–8

445 54 Rizvi, S.Z.M. *et al.* (2015) Influence of *Botrytis cinerea* (Helotiales:
446 *Sclerotiniaceae*) infected leaves of *Vitis vinifera* (Vitales: Vitaceae) on the

447 preference of *Epiphyas postvittana* (Lepidoptera: Tortricidae). *Austral Entomol.*
448 54, 60–70

449 55 Friman, V.-P. and Buckling, A. (2014) Phages can constrain protist predation-
450 driven attenuation of *Pseudomonas aeruginosa* virulence in multienemy
451 communities. *ISME J.* 8, 1820–1830

452 56 Dargent, F. *et al.* (2013) Experimental elimination of parasites in nature leads
453 to the evolution of increased resistance in hosts. *Proc. R. Soc. B Biol. Sci.* 280,
454 57 Adams, J. and Rosenzweig, F. (2014) Experimental microbial evolution: history
455 and conceptual underpinnings. *Genomics* 104, 393–398

456 58 de Vienne, D.M. *et al.* (2013) Cospeciation vs host-shift speciation: methods for
457 testing, evidence from natural associations and relation to coevolution. *New*
458 *Phytol.* 198, 347–385

459 59 Longdon, B. *et al.* (2014) The Evolution and Genetics of Virus Host Shifts.
460 *PLoS Pathog.* 10, 1–8

461 60 Cuthill, J.H. and Charleston, M.A. (2013) A Simple Model Explains the
462 Dynamics of Preferential Host Switching Among Mammal Rna Viruses.

463 *Evolution* 67, 980–990

464 61 Araujo, S.B.L. *et al.* (2015) Understanding Host-Switching by Ecological Fitting.

465 *PLoS One* 10, e0139225

466 62 Campisano, A. *et al.* (2014) Interkingdom transfer of the acne-causing agent,

467 *Propionibacterium acnes*, from human to grapevine. *Mol. Biol. Evol.* 31, 1059–

468 1065

469 63 Allison, A.B. *et al.* (2012) Role of Multiple Hosts in the Cross-Species

470 Transmission and Emergence of a Pandemic Parvovirus. *J. Virol.* 86, 865–872

471 64 Crill, W.D. *et al.* (2000) Evolutionary Reversals During Viral Adaptation to
472 Alternating Hosts. *Genetics* 154, 27–37

473 65 Longdon, B. *et al.* (2015) The Causes and Consequences of Changes in
474 Virulence following Pathogen Host Shifts. *PLoS Pathog.* 11, 1–18

475 66 Longdon, B. *et al.* (2011) Host Phylogeny Determines Viral Persistence and
476 Replication in Novel Hosts. *PLoS Pathog.* 7, 1–9

477 67 Woolhouse, M.E.J. *et al.* (2005) Emerging pathogens : the epidemiology and
478 evolution of species jumps. *Trends Ecol. Evol.* 20, 238–244

479 68 Poullain, V. *et al.* (2012) Infection Genetics and the Likelihood of Host Shifts in
480 Coevolving Host-Parasite Interactions. *Am. Nat.* 180, 618–628

481 69 Thrall, P.H. *et al.* (2016) Epidemiological and Evolutionary Outcomes in Gene-
482 for-Gene and Matching Allele Models. *Front. Plant Sci.* 6, 1–12

483 70 Dybdahl, M.F. and Storfer, A. (2003) Parasite local adaptation : Red Queen
484 versus Suicide King. *Trends Ecol. Evol.* 18, 523–530

485 71 McNally, L. *et al.* (2014) Cooperative secretions facilitate host range expansion
486 in bacteria. *Nat. Commun.* 5, 4594

487 72 Di Giallonardo, F. and Holmes, E.C. (2015) Viral biocontrol: grand experiments
488 in disease emergence and evolution. *Trends Microbiol.* 23, 83–90

489 73 Williams, P.D. *et al.* (2014) Evidence of trade-offs shaping virulence evolution
490 in an emerging wildlife pathogen. *J. Evol. Biol.* 27, 1271–1278

491 74 Kerr, P.J. *et al.* (2012) Evolutionary history and attenuation of myxoma virus on

492 two continents. *PLoS Pathog.* 8, e1002950

493 75 Johnson, P.T.J. *et al.* (2013) Biodiversity decreases disease through
 494 predictable changes in host community competence. *Nature* 494, 230–233

495 76 Bedhomme, S. *et al.* (2012) Multihost experimental evolution of a plant RNA
 496 virus reveals local adaptation and host-specific mutations. *Mol. Biol. Evol.* 29,
 497 1481–1492

498 77 Guidot, A. *et al.* (2014) Multihost Experimental Evolution of the Pathogen
 499 *Ralstonia solanacearum* Unveils Genes Involved in Adaptation to Plants. *Mol.*
 500 *Biol. Evol.* 31, 2913–2928

501 78 Poullain, V. and Nuismer, S.L. (2012) Infection Genetics and the Likelihood of
 502 Host Shifts in Coevolving Host-Parasite Interactions. *Am. Nat.* 180, 618–628

503 79 Dillon, R.J. *et al.* (2005) Diversity of locust gut bacteria protects against
 504 pathogen invasion. *Ecol. Lett.* 8, 1291–1298

505 80 Dong, Y. *et al.* (2009) Implication of the mosquito midgut microbiota in the
 506 defense against malaria parasites. *PLoS Pathog.* 5, 1–10

507 81 Jaenike, J. *et al.* (2010) Adaptation via symbiosis: recent spread of a
 508 *Drosophila* defensive symbiont. *Science* 329, 212–215

509 82 Koch, H. and Schmid-Hempel, P. (2011) Socially transmitted gut microbiota
 510 protect bumble bees against an intestinal parasite. *Proc. Natl. Acad. Sci. U. S.*
 511 *A.* 108, 19288–92

512 83 Arnold, A.E. *et al.* (2003) Fungal endophytes limit pathogen damage in a
 513 tropical tree. *Proc. Natl. Acad. Sci. U. S. A.* 100, 15649–15654

514 84 Mendes, R. *et al.* (2011) Deciphering the rhizosphere microbiome for disease-

515 suppressive bacteria. *Science* 332, 1097–1100

516 85 May, G. and Nelson, P. (2014) Defensive mutualisms: Do microbial interactions
517 within hosts drive the evolution of defensive traits? *Funct. Ecol.* 28, 356–363

518 86 Kamada, N. *et al.* (2013) Role of the gut microbiota in immunity and
519 inflammatory disease. *Nat. Rev. Immunol.* 13, 321–35

520 87 Haine, E.R. (2008) Symbiont-mediated protection. *Proc. R. Soc. B Biol. Sci.*
521 275, 353

522 88 Gerardo, N.M. and Parker, B.J. (2014) Mechanisms of symbiont-conferred
523 protection against natural enemies: An ecological and evolutionary framework.
524 *Curr. Opin. Insect Sci.* 4, 8–14

525 89 Parker, B.J. *et al.* (2011) Non-immunological defense in an evolutionary
526 framework. *Trends Ecol. Evol.* 26, 242–248

527 90 Vavre, F. and Charlat, S. (2012) Making (good) use of *Wolbachia*: What the
528 models say. *Curr. Opin. Microbiol.* 15, 263–268

529 91 Ford, S.A. and King, K.C. (2016) Harnessing the Power of Defensive Microbes:

537 94 Martinez, J. *et al.* (2016) Addicted ? Reduced host resistance in populations

530 Evolutionary Implications in Nature and Disease Control. *PLOS Pathog.* 12,
531 e1005465

532 92 Afkhami, M.E. *et al.* (2014) Multiple mutualist effects: conflict and synergy in
533 multispecies mutualisms. *Ecology* 95, 833–844

534 93 Strauss, J.F. and Telschow, A. (2015) Modeling the indirect effect of *Wolbachia*
535 on the infection dynamics of horizontally transmitted viruses. *Front. Microbiol.*
536 6, 1–9

537 94 Martinez, J. *et al.* (2016) Addicted ? Reduced host resistance in populations

538 with defensive symbionts. *Proc. R. Soc. B Biol. Sci.* 283, 1–10

539 95 Koch, H. and Schmid-Hempel, P. (2012) Gut microbiota instead of host
540 genotype drive the specificity in the interaction of a natural host-parasite
541 system. *Ecol. Lett.* 15, 1095–1103

542 96 Rouchet, R. and Vorburger, C. (2012) Strong specificity in the interaction
543 between parasitoids and symbiont-protected hosts. *J. Evol. Biol.* 25, 2369–
544 2375

545 97 Rouchet, R. and Vorburger, C. (2014) Experimental evolution of parasitoid
546 infectivity on symbiont-protected hosts leads to the emergence of genotype
547 specificity. *Evolution* 68, 1607–1616

548 98 Kwiatkowski, M. *et al.* (2012) On genetic specificity in symbiont-mediated host-
549 parasite coevolution. *PLoS Comput. Biol.* 8, e1002633

550 99 Harcombe, W.R. *et al.* (2016) Adding Biotic Complexity Alters the Metabolic
551 Benefits of Mutualism. *Evolution* DOI:10.1111/evo.12973

552 100 Harcombe, W. (2010) Novel cooperation experimentally evolved between
553 species. *Evolution* 64, 2166–72

554 101 Harcombe, W.R. *et al.* (2014) Metabolic Resource Allocation in Individual
555 Microbes Determines Ecosystem Interactions and Spatial Dynamics. *Cell Rep.*
556 7, 1104–1115

557 102 Ferrière, R. *et al.* (2007) Evolution and persistence of obligate mutualists and
558 exploiters: Competition for partners and evolutionary immunization. *Ecol. Lett.*
559 10, 115–126

560 103 Alizon, S. *et al.* (2013) Multiple infections and the evolution of virulence. *Ecol.*

561 *Lett.* 16, 556–567

562 104 Koskella, B. *et al.* (2012) The costs of evolving resistance in heterogeneous
563 parasite environments. *Proc. R. Soc. B Biol. Sci.* 279, 1896–903

564 105 Örmälä-Odegrip, A.-M. *et al.* (2015) Protist predation can select for bacteria
565 with lowered susceptibility to infection by lytic phages. *BMC Evol. Biol.* 15, 1–7

566 106 Friman, V.-P. and Buckling, A. (2013) Effects of predation on real-time host-
567 parasite coevolutionary dynamics. *Ecol. Lett.* 16, 39–46

568

OUTSTANDING QUESTIONS BOX

- ***How does community diversity affect host-parasite coevolutionary***

dynamics? When parasites and hosts coevolve in a pairwise framework, a pattern may emerge which indicates the nature of the underlying dynamics (e.g. arms race vs. red queen dynamics). In a complicated network, a single parasite or host species coevolving with multiple players may display different dynamics at different loci (e.g. one locus could be the focus of selection for coevolution with a host and another in coevolution with competitors). The way diversity affects the nature of coevolution between host and parasites remains an important unanswered question.

- **What are the effects of combining biotic and abiotic gradients on host-**

parasite interactions? Abiotic gradients or fluctuations, such as changes in nutrients, temperature, and pH are common in natural habitats and can alter the nature of interactions within a community. There have been many recent studies that have incorporated abiotic gradients or fluctuations built around a pairwise host-parasite interaction. There is enormous potential in combining greater biotic diversity with abiotic fluctuations towards a better understanding of the dynamics that emerge in natural systems.

- **How does biotic diversity effect host and parasite evolutionary rates?**

Theory predicts that adding a defensive mutualist to a focal host-parasite relationship might reduce the rate of coevolution with the host as the mutualist takes over as the primary antagonist for the parasite. Likewise, an extra parasite introduces between-parasite competition, which could rapidly drive the evolution of parasite life history traits and increase parasite evolutionary rates.

