

Grand Challenges in Coevolution

Mónica Medina^{1*}, David M. Baker², David Baltrus³, Gordon M. Bennett⁴, Ulisse Cardini⁵, Adrienne M. Correa⁶, Sandie M. Degnan⁷, Gregor Christa⁸, Eunsoo Kim⁹, Jingchun Li¹⁰, David R. Nash¹¹, Ezequiel M. Marzinelli¹², Michele K. Nishiguchi¹³, Carlos Prada¹⁴, Melissa S. Roth¹⁵, Mahasweta Saha¹⁶, Christopher I. Smith¹⁷, Kevin R. Theis¹⁸, Jesse R. Zaneveld¹⁹

¹Department of Biology, The Pennsylvania State University (PSU), United States, ²School of Biological Sciences, The University of Hong Kong, Hong Kong, SAR China, ³School of Plant Sciences, University of Arizona, United States, ⁴Department of Life and Environmental Sciences, University of California, Merced, United States, ⁵Department of Integrated Marine Ecology, Zoological Station Anton Dohrn, Department of Biology, Polytechnic and Basic Sciences School, University of Naples Federico II, Italy, ⁶BioSciences Department, Rice University, United States, ⁷School of Biological Sciences, The University of Queensland, Australia, ⁸Institute of Zoology, University of Jüppertal, Germany, ⁹Division of Invertebrate Zoology and Sackler Institute of Comparative Genomics, American Museum of Natural History, United States, ¹⁰Department of Ecology and Evolutionary Biology, University of Colorado Boulder, United States, ¹¹Department of Biology, University of Copenhagen, Denmark, ¹²School of Life and Environmental Sciences, Institute of Agriculture, The University of Sydney, Australia, ¹³Department of Molecular and Cell Biology, University of California, Merced, United States, ¹⁴Department of Biological Sciences, University of Rhode Island, United States, ¹⁵Department of Plant and Microbial Biology, University of California, Berkeley, United States, ¹⁶Marine Ecology and Biodiversity, Plymouth Marine Laboratory, United Kingdom, ¹⁷Department of Biology, Willamette University, United States, ¹⁸Department of Biochemistry, Microbiology & Immunology, Wayne State University, United States, ¹⁹Division of Biological Sciences, School of Science Technology Engineering and Math, University of Washington Bothell, United States

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Contribution to the field

This Grand Challenge highlights current topics, debates, and standing questions in the field of evolution. Coevolutionary biology has experienced a major increase in interest due to the explosion of microbiome research across the Tree of Life. Thanks to advances in omics technologies, coevolution research has gone from focusing on macroorganismal to host-microbiome interactions opening avenues of intellectual pursuit to develop new conceptual frameworks. The authors hope to entice contributions to the section that address questions dealing with both traditional two-partner interactions to coevolutionary networks.

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Mahasweta Saha¹⁶, Christopher I. Smith¹⁷, Kevin Theis¹⁸, Jesse Zaneveld¹⁹

¹Department of Biology, Pennsylvania State University, University Park PA, USA

²School of Biological Sciences & Swire Institute of Marine Science, The University of Hong Kong, Pokfulam, Hong Kong, PRC

³School of Plant Sciences, University of Arizona, Tucson AZ, USA

⁴Department of Life and Environmental Sciences, University of California Merced, Merced CA, USA

⁵Integrative Marine Ecology Department, Stazione Zoologica Anton Dohrn - National Institute of Marine Biology, Ecology and Biotechnology, Napoli, Italy

⁶BioSciences Department, Rice University, Houston, TX, USA

⁷School of Biological Sciences, University of Queensland, Brisbane QLD, Australia

⁸Institute of Zoology, University of Wuppertal, Wuppertal, Germany

⁹Division of Invertebrate Zoology and Sackler Institute of Comparative Genomics, American Museum of Natural History, New York NY, USA

¹⁰Department of Ecology and Evolutionary Biology, University of Colorado Boulder, Boulder, CO, USA

¹¹Department of Biology, University of Copenhagen, Copenhagen, Denmark

¹²The University of Sydney, School of Life and Environmental Sciences, Sydney, NSW 2006, Australia

¹³Department of Molecular and Cell Biology, University of California Merced, Merced, CA, USA

¹⁴Department of Biological Sciences University of Rhode Island, RI, USA

¹⁵Department of Plant and Microbial Biology, University of California, Berkeley, CA, USA

¹⁶Marine Ecology and Biodiversity, Plymouth Marine Laboratory, Prospect Place, PL1 3DH, Plymouth, United Kingdom.

¹⁷Department of Biology, Willamette University, Salem OR, USA

¹⁸Department of Biochemistry, Microbiology & Immunology, Wayne State University School of Medicine, Detroit MI, USA

¹⁹Division of Biological Sciences, School of Science Technology Engineering and Math, University of Washington Bothell, Bothell WA, USA

*** Correspondence:**

Mónica Medina

momedinamunoz@gmail.com

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Coevolution – reciprocal evolutionary change between interacting lineages (Thompson 1994; see glossary) – is thought to have played a profound role in the evolution of Life on Earth. From similar patterns across the wings of unrelated lineages of butterflies (Hoyal Cuthill and Charleston 2015), egg mimicry of “cheating” brood parasites (Davies, 2010), to the role of animal pollinators in driving the diversification flowering plants (Kay and Sargent 2009), to the ubiquity of sexual reproduction (and sexual conflicts (Hamilton, 2002; Arnqvist and Rowe, 2005; King et al., 2009), the formation of the eukaryotic cell (Martin et al. 2015; Imachi et al. 2020), and even the origin of living organisms themselves (Mizuuchi and Ichihashi 2018), evolutionary changes among interacting lineages have played profound and important roles in the history of Life.

This Grand Challenges inaugural contribution encompasses eclectic opinions of the editorial board as to what are the next frontiers of coevolution research in the 21st century. Coevolutionary biology is a field that has garnered a lot of attention in recent years, in part as a result of technical advances in nucleotide sequencing and bioinformatics in the burgeoning field of host-microbial interactions. Many seminal studies of coevolution examined reciprocal evolutionary change between two or a few interacting macroscopic species that imposed selective pressures on one another (e.g., insect or bird pollinators and their flowering host plants). Understanding the contexts under which coevolution occurs, as opposed to scenarios in which each partner adapts independently to a particular environment (Darwin 1862; Stiles 1978) is important to elucidate coevolutionary processes. A whole spectrum of organismal interactions has been examined under the lens of coevolution, providing additional context and nuance to ecological strategies traditionally categorized as ranging from beneficial to detrimental for participating species (Figure 1). In particular, a coevolutionary perspective has revealed that even ‘mutualisms’ are not always fully beneficial or cooperative for the partners involved. Instead, the tendency to ‘cheat’ permeates across symbiotic partnerships (Perez-Lamarque et al. 2020). Conversely, recent evidence suggests that non-lethal predation by co-evolved predators, which has traditionally been assumed to be entirely antagonistic, may provide sessile prey with some indirect benefit through enhanced opportunities to acquire beneficial symbiotic microorganisms (Grupstra et al. 2020). Herein we discuss some of the recent areas of active research in coevolution, restricting our focus to coevolution between interacting species.

Coevolution and diversification

Among multicellular eukaryotes, an enduring question is whether interactions between organisms have played a role in promoting speciation and diversification over evolutionary time (Thompson 1989; Althoff et al. 2014; Hembry et al. 2014; Maron et al. 2019). Naturalists have argued since the 19th century that interactions with pollinators may have spurred the dramatic and rapid diversification of flowering plants (Grant 1949; Friedman 2009). Similarly, Ehrlich and Raven, who first coined the term “coevolution,” argued that the origin of novel defensive chemicals in members of the Apiaceae (plants in the carrot family) may have served as ‘key innovations’ that allowed them to avoid plant-feeding insects and colonize new habitats. Herbivorous insects that evolved compensatory mechanisms to tolerate or neutralize these toxins could then have recolonized these plants and, freed from competition with other insects, themselves diversified (Ehrlich and Raven 1964). Patterns at a macroevolutionary scale offer multiple lines of evidence to support these conjectures. The diversification of flowering plants in the Jurassic and Cretaceous eras coincided with the diversification of pollinators (Grimaldi 1999), followed by the evolution of herbivorous insects that specialized on flowering plants (Farrell 1998). Further corroborating coevolution as a driver of diversification, these insects that feed on flowering plants are vastly more diverse than those that are frequented by generalist pollinators (Mitter et al. 1988; Farrell 1998), even when controlling for time. Additionally, plants that rely on specialized pollinators are more diverse than those with generalized pollinators (Dodd et al. 1995; Sargent 2003; Kay and Sargent 2009). Finally, species that have particularly strong or highly specialized ecological interactions, such as hosts and parasites or plants and insects involved in obligate pollination mutualisms, often show patterns of **‘phylogenetic congruence’** – for example any particular species of parasite is often most closely related to parasites that feed on their host’s nearest relatives (Page 1996; Paterson et al. 2000; Weiblen 2004).

However, connecting these broadscale patterns to evolutionary and ecological mechanisms, and specifically evaluating the role of coevolution at the microevolutionary scale in generating diversity at a macroevolutionary level remains a major challenge (Hembry et al. 2014). Theoretical treatments have made different predictions about the circumstances under which reciprocal natural selection may promote evolutionary divergence and reproductive isolation (Kiestler et al. 1984; Yoder et al. 2010), and empirical studies have produced contradictory results. Whereas early work suggested that mutualistic interactions such as those between plants and their pollinators could prompt speciation, more recent modelling work suggests that mutualisms are more likely to promote evolutionary stasis (Yoder and Nuismer 2010). Predominantly antagonistic interactions on the other hand can promote evolutionary divergence at a population-level, depending on the factors that mediate the fitness of each player. In cases of escalating coevolution – in which predators and prey evolve ever stronger defenses and counter defenses – rapid divergence in phenotypes between populations may arise (Brodie et al. 2002; Brodie and Ridenhour 2003). For example, among brood parasites like cuckoos that lay their eggs in the nests of other birds, the cuckoos experience natural selection that more and more

120 closely matches the coloration and patterning of their eggs to those of their local hosts
121 (Spottiswoode and Stevens 2012). The birds whose nests are parasitized by cuckoos in turn
122 rapidly evolve more complex patterning in their own eggs (Yang et al. 2010; Spottiswoode and
123 Stevens 2012). Host birds may also experience enhanced capacity to recognize and expel the
124 eggs of their cuckoo parasites (Soler et al. 2001). However, populations that occur in regions
125 where the cuckoo is absent fail to eject even grossly mismatched eggs (Soler and Møller 1990).
126 There is contradictory evidence, however, as to whether arms-race coevolution of this type
127 results in greater rates of diversification (Smith and Benkman 2007; Krüger et al. 2009; Fossøy
128 et al. 2016).

129
130 To generate empirical evidence that coevolution per se is the causal mechanism of
131 diversification, another challenge, and perhaps a more fundamental one, is ruling out alternative
132 explanations of diversification (Althoff et al. 2014). Patterns suggestive of reciprocal adaptation
133 can arise through adaptation by one of the two interacting species alone (that is, natural selection
134 without reciprocal adaptation), or even through neutral processes that do not involve selection at
135 all (Janzen 1980; Yoder and Nuismer 2010). Patterns of phylogenetic congruence, for example,
136 may be the product of a common biogeographic history rather than ‘cospeciation’ (Smith et al.
137 2008; Althoff et al. 2012, 2016) and the greater diversity of organisms that are involved in
138 specialized interactions might not indicate that the interactions themselves prompted higher rates
139 of speciation (Armbruster and Muchhala 2009). ‘Phenotype matching’ – correlations in the
140 features of interacting species such as floral structures that match features of their pollinators
141 (Nilsson 1988) or defenses against predators that are met by equally strong counter defenses
142 (Brodie and Ridenhour 2003) – although often taken as evidence for coevolution can arise due to
143 extrinsic forces, or even through simple genetic drift (Nuismer et al. 2010). Finally, selection by
144 climate, edaphic soil factors, and other extrinsic forces may be more important than coevolution
145 per se in driving divergence between populations (Nuismer and Gandon 2008).

146
147 This difficulty in reconciling compelling macroevolutionary patterns that suggest coevolution
148 drives speciation in eukaryotes with the paucity of evidence at the ecological and
149 microevolutionary scale thus constitutes a ‘grand challenge’ in coevolution.

150 151 152 **The complexity of the holobiont complicates coevolutionary analysis**

153
154 An additional, newer ‘grand challenge’ stems from the emerging realization that every
155 macroorganism is actually a holobiont – a host organism together with all of the resident
156 microorganisms living on or in it symbiotically. Thus, virtually every coevolutionary interaction
157 has the potential to represent a diffuse or guild coevolution, in which a single species co-evolves
158 with a **guild** and/or two guilds coevolve (e.g., Janzen 1980), rather than a two-partner
159 interaction. Studying diffuse interactions is inherently more challenging than two-partner

interactions because of the higher number of entities (and their potential interactions) involved. Further, when many partners are involved (e.g. in a **holobiont**), each partner will have its own generation time, mutation rate and specific biology, adding additional complexity. Yet research effort directed towards diffuse interactions (e.g., (Matthews et al. 2020)) has become common practice due to increased research in host-microbiome interactions across many taxa. As a consequence, there is a need to expand our conceptual coevolutionary framework, and we focus primarily on complex coevolutionary networks in this grand challenge paper. Given that such challenges increase exponentially in more complex coevolving assemblages, it is important to discriminate between interactions that represent outcomes of coevolution versus those that are outcomes simply of evolution. We therefore focus our grand challenge primarily on complex coevolutionary networks. Building such a framework will require integrating the jargon (e.g., **microbiome**) and concepts – such as the **holobiont** (Margulis and Fester 1991; Bordenstein and Theis 2015) and the **hologenome** (Collens et al. 2019) – of microbial ecology with those of the broader coevolutionary literature. It will further require the development of reliable tests for coevolution at multiple scales of biological organization (e.g. coevolution at the gene, genome, metabolic and organismal levels). Holobionts can, therefore, be thought of as interacting community members that are best visualized as complex networks highly specific to diffuse interactions (Bascompte 2019). All partners may be genuinely coevolving, or each may be independently adapting to (shared) selective pressures in their own (shared) environments. Alternatively, a holobiont may be a mixture of both (Bordenstein and Theis 2015). The role of coevolutionary research is to discriminate between independent evolution and coevolution, so that we can position core members versus transient members along a coevolutionary spectrum. The selective forces shaping coevolving organisms are different from those in independently evolving but codiversifying taxa. Coevolutionary networks are dynamic, and depending on the types of interactions nested within them, and the extent of external perturbations (e.g. climate change), they can lead to different diversification outcomes (Thompson 2006) (Figure 2).

It is well established that microbes affect the physiology and development of most if not all eukaryotic organisms (Gilbert and Epel 2015; Gilbert et al. 2015; Peixoto et al. 2021). Although it is tantalizing to imagine if and how these microbes have coevolved with both unicellular and multicellular eukaryotic hosts, and to make assumptions about evolutionary processes underlying noticeable patterns in community structures, we still lack a basic framework for testing whether host-microbiome coevolution has occurred. One area that is worth exploring involves the ongoing endosymbiosis among eukaryotic or prokaryotic partners, where complimentary genomic and metabolic functional reductions can be assessed. For example, some diatoms have incorporated cyanobacterium that performs nitrogen fixation, and the cyanobacterium has since lost its photosynthetic ability (Nakayama et al. 2014). Similar processes have been repeatedly observed in lichens (Pogoda et al. 2018). Even in experimental evolution systems involving pairs of microbes, rigorous tests of coevolution (e.g. using time-shift pairings of ancestral vs. evolved partners) are major undertakings with many technical challenges (e.g., Hillesland and Stahl

200 2010). We propose a general consensus for coevolutionary theory that requires phenotypic
201 changes in coevolving organisms (or guilds) to influence fitness in a reciprocal matter. The field
202 will need to demand specific and sufficient evidence to demonstrate that host-microbiome
203 coevolution is indeed happening. The nature of evidence sufficient to demonstrate such
204 coevolution also still needs to be determined. The development of a standardized set of tools to
205 evaluate the potential for coevolution across hosts, as well as the creation and elaboration of
206 neutral models for microbiome community assembly and evolution in the absence of
207 coevolution, will support the development of a framework for testing for host-microbiome
208 coevolution. Detailing the nature of what constitutes sufficient evidence, and of a standardized
209 tool set, is outside the scope of this opinion piece. Unravelling eco-evolutionary processes
210 (Blasco-Costa et al., 2021) propose the use of interaction trait codependency as well as
211 geographical network modularity to shed light in the mechanisms driving, or not, coevolutionary
212 processes. We encourage the coevolution community to build new analytical tools that combine
213 community assembly theory with cophylogenetic theory (e.g., Russo et al., 2018).

214 215 216 **Different spatio-temporal scales offer a variety of perspectives on coevolution in holobionts**

217
218 The definition of symbiosis across research fields ranging from microbiology to ecology
219 sometimes differ, reflecting the emphases on different types of interactions. Herein we use the
220 original definition of **symbiosis** (De Bary 1879; Oulhen et al. 2016), thus one should not assume
221 *a priori* that all (or indeed any) symbiotic (i.e. coresident) partners in a holobiont are coevolving.
222 In intimate interactions that require metabolic complementarity, understanding the dynamics of
223 species coupling (e.g., horizontally vs. vertically transmitted symbionts) over ontogeny is
224 paramount to be able to develop coevolutionary models that incorporate the molecular
225 underpinnings of fitness in all partners (Roughgarden et al. 2018; Lloyd and Wade 2019; Correa
226 et al. 2021). Ecological theory has developed concepts such as **facilitation** to describe
227 predominantly positive species interactions (Bruno et al. 2003). Symbiotic organisms are often
228 coevolving and can also be understood in a framework of the evolution of cooperation (Herre et
229 al. 1999; Kiers and Van Der Heijden 2006). Other well-established ecological theories may be
230 applicable where negative coevolutionary interactions are involved (e.g., host-parasite). The
231 main idea is that coevolving groups may represent a single unit of selection. A healthy debate
232 has been taking place in the literature, that moves beyond absolutist views of pure independence
233 (e.g., no cooperation) or pure interdependence (e.g. the full holobiont as the unit of selection) in
234 fitness, and instead increasingly asks to what degree, and in which direction (e.g., predominantly
235 mutualism vs. commensalism vs. parasitism) and under what conditions holobiont members
236 coevolve (Herre et al. 1999; Bordenstein and Theis 2015; Moran and Sloan 2015; Lloyd and
237 Wade 2019). If a lineage of microbes has codiversified with its host over evolution,
238 coevolutionary research should aim to determine whether those microbes are more likely to be

'keystone species' serving a set of 'core' functions or whether there is convergence in the set of microbial functions rather than organismal coevolution (Doolittle and Inkpen 2018).

Stressors often alter the temporal or interindividual variability in the microbiome. The literature on how and why microbiomes vary with stress offers contrasting predictions for how these changes influence host health and fitness. On the one hand, if microbiomes are tightly regulated by their host (even during physiological stress), variability in the microbiome in the face of stress might represent 'fine-tuning' of the microbiome to better cope with that stress (e.g. the coral probiotic hypothesis) (Reshef et al. 2006). Conversely, physiological stress could produce microbiome variance by reducing the ability of the host to regulate its microbiome, a process coined as the Anna Karenina Principle (AKP) (Zaneveld et al. 2017). Under the AKP, microbiome variance during physiological stress may represent a loss of host control that could be neutral or harmful for host health. Another possibility is that microbial contributions to holobiont function could vary based on the holistic composition of microbes present, due to facilitative or competitive interactions (e.g., McIlroy et al. 2019) arising due to complementarity effects (Tilman et al. 1997; Loreau 1998; Fox 2005). Empirically testing these contrasting predictions with diverse hosts, microbial groups (e.g., Claas et al. 2020; Howe-Kerr et al. 2020) and stressors may paint a more complete picture of what happens when stress perturbs holobiont dynamics, yet specific attention needs to be given to whether stress-driven outcomes are the result of coevolving taxa.

A key concept investigated in evolution is adaptive **phenotypic plasticity** and how it can generate fixed traits through genetic assimilation of alternative phenotypes (Schlichting and Pigliucci 1998; West-Eberhard 2003; Pigliucci and Muller 2010). The subset of symbionts that organisms have at the present time may come from a much larger pool that was available to their ancestors and then later can become fixed (Waddington 1953; West-Eberhard 2003; Lande 2009). The ability to establish relationships with symbiotic partners could therefore be plastic, depending on lineage-specific environmental and historical factors; this can be tested by applying phylogenetic tools and sampling enough partners. Phylogenetic inference will also assist in understanding whether symbiotic interactions that often result in coevolutionary patterns can arise equally often from mutualistic, commensalistic and parasitic relationships (Thompson and Fernandez 2006). It is still uncertain under what conditions coevolving taxa act as mutualists and under what conditions they become parasitic (e.g., Baker et al. 2018) or pathogenic (Lesser et al. 2013; Correa et al. 2021). The driving pressures governing each type of interaction, and the plasticity to move between those types of interactions, remain unknown. Nonetheless, phenotypic plasticity provides a mechanism to understand 'fixed' relationships. The evolution of eusociality provides a good example. Once eusociality evolves, social and solitary behaviors can be fixed in species or populations back and forth by expressing preexisting alternative phenotypes via developmental switches that are turned on and off depending on the ecological/environmental context (Field et al., 2010). Developmental plasticity thus provides a

robust framework to understand the labile phylogenetic pattern of fixation of solitary and social behaviors and the traits that facilitate them (Wittwer et al., 2017) across species in many insect groups.

With respect to microbiomes, there is a considerable challenge in isolating individual species to ascertain their function (McIlroy et al. 2020). Metabolic versatility is accomplished in holobionts thanks to the simultaneous occurrence of disparate biochemical machineries of symbionts, whose roles within the host can convergently evolve (e.g., McCutcheon et al. 2009). However, we still lack an understanding of the biogeochemical and ecological functions, as well as the establishment and maintenance, of many of these relationships (Beinart 2019). This is despite these functional relationships likely contributing in an important way to the flows of energy and matter within their ecosystem (e.g., Thurber et al. 2017; Cardini et al. 2019; Zimmerman et al. 2020), and across spatial and organizational scales (Pita et al. 2018). It becomes important to investigate to what extent coevolution within and among holobionts is an agent of ecosystem change.

Molecular coevolution

Organisms that engage in coevolutionary interactions impose reciprocal selection that should leave molecular signatures (e.g., horizontal gene transfer, natural selection) across their genomes. Until recently, it remained challenging to explicitly test questions of the genetic mechanisms that underlie coadapted organismal complexes, due to difficulties in identifying all interacting organisms and assaying entire genomes for signatures of selection. Advances in multi-omics technologies provide the capabilities to test specific hypotheses of how interacting organisms shape each other's genomes (e.g., Degnan 2014). For example, in obligate animal-bacterial symbioses, full-genome sequencing has revealed that the genomes of bacterial symbionts are shaped by the host environment, often leading to metabolic specialization and extreme genome size reduction (reviewed in McCutcheon and Moran 2012). In order to manage and sustain these relationships, animal hosts are known to evolve specialized organs that deliver tailored support by reprogramming the expression of thousands of eukaryotic genes (Hansen and Moran 2011; Belcaid et al. 2019). Some of these support genes evolved from the duplication of existing host genes, the repurposing of genes that supported more ancient symbioses (e.g., mitochondria), or the horizontal transfer of bacterial genes to the host nuclear genomes (Husnik et al. 2013; Sloan et al. 2014; Mao et al. 2018). When different organisms live in close contact with each other, this can lead to molecular interactions (e.g., protein-protein, protein-nucleic acids) of different origins. Coevolutionary research should investigate the consequences of such interactions and whether they offer an opportunity for metabolic innovation (and not simply the transfer of a metabolic module) that may otherwise be difficult to attain by mutations or lateral transfer of individual genes (rather than simply the transfer of a metabolic module). Investigation

into the metabolic aspects of eukaryogenesis, which involved interactions of two or more microbial species, as well as the evolution of eukaryotic photosynthesis, may provide a historical context for the re-wiring of interactome and regulatory networks in symbioses (e.g., Burns et al. 2018; Leitão et al. 2020)

Recognizing Homology and Homoplasy in the Evolution of Symbiosis

In cases where coevolution is repeatable, one untested prediction is that phenotypic traits will emerge when two or more organisms interact in an intricate matter. A classic example is the case of photosymbiosis. Multiple photosynthetic microbial taxa (e.g., cyanobacteria, green algae, dinoflagellate algae) established mainly endosymbiotic symbiosis with diverse heterotrophic eukaryotic hosts including fungi (e.g., lichens), unicellular protists (e.g. *Chlorella*-bearing ciliates, foraminifera, mixotrophic testate amoebae) (Hallock 1999; Preisfeld et al. 2011; Gomaa et al. 2014), and animals (e.g., reef-building corals, *Hydractinia* group of *Hydra*) (Stanley 2006; Kawaida et al. 2013; van Oppen and Medina 2020). Understanding whether the same molecular machinery is involved in establishing and maintaining photosymbiosis each time, poses interesting questions about when we should consider a trait as homologous versus convergent (Stoeckert et al. 2009; Medina-Lavado et al. 2018; Li et al. 2020). Studying similar types of symbioses across diverse organisms will lend itself not only to mechanistic discoveries, but also to advancing conceptual debates. In morphological evolution, shared traits that are homologs often show important mechanistic similarities that are not shared in convergently evolved traits (Scotland 2010). During holobiont evolution, animal-microbe or plant-microbe symbioses may persist through evolution or may evolve convergently. A major goal in coevolutionary research will be to distinguish homologous symbioses from homoplasies to elucidate if the same patterns extend to different underlying molecular mechanisms. Although the molecular mechanisms regarding many symbioses still await elucidation, preliminary data show that convergently evolved symbiotic associations sometimes display the same molecular level adaptations. For example, both corals (Cnidaria) and giant clams (Mollusca) are known to host algae from the family Symbiodiniaceae (Trench 1979), although the symbiosis is intracellular for corals (Davy et al. 2012) and extracellular for the bivalves (Ip and Chew 2021). However, these two distantly related animal lineages both utilize the vacuolar H⁺-ATPase gene (*VHA*) to acidify their symbiont-containing environments, thereby facilitating the carbon concentrating process, and promoting algal photosynthesis (Barott et al. 2015; Armstrong et al. 2018). *VHA* is a highly conserved gene in eukaryotes (Anraku et al. 1992), and neither host lineages possesses “special” versions of *VHA* compared to their non-symbiotic relatives (Li et al. 2020). Therefore, adaptations to photosymbiosis appear to have occurred at the regulatory/expression level, specifically by expressing *VHA* in the symbiont-containing cells/tissues (Barott et al. 2015; Armstrong et al. 2018). This example indicates that molecular-level parallel evolution can occur in convergently evolved symbiosis. Future research efforts are

needed to examine this phenomenon, and special attention needs to be paid to gene regulatory mechanisms.

Microbiomes can influence the evolution of host behavioral traits

Mounting evidence suggests that animal behavioral phenotypes can be influenced by the microbiome (Archie and Theis 2011; Ezenwa et al. 2012; Zhu et al. 2018; Vernier et al. 2020). Specifically, the microbiome can contribute to host anti-predator behaviors, increase host foraging efficiency and reproductive output, and mediate host communication (Theis et al. 2020). In some instances, for example in the bioluminescence-enabled camouflaged antipredator behavior of bobtail squids, a single microbial symbiont, *Vibrio fischeri*, contributes directly to a host behavioral phenotype that is under strong selective pressure. However, in other cases, such as mammals scent marking with secretions from specialized integumental scent glands, a diverse suite of microbial symbionts appears to contribute behaviorally-relevant components to the chemical signaling phenotypes of their hosts. Hypotheses such as this are ample fodder for elucidating the intricacies of the proximate and ultimate relationships between hosts and their various symbionts in specific organs and among the symbionts themselves in generating the complex phenotypes of holobionts (Côté et al., 2018). For instance, if the holobiotic hypothesis for animal chemical communication is correct, then: 1) scent organs should harbor odor-producing microbes that exhibit phylosymbiosis across host clades; 2) both the microbial and odor profiles of these organs should vary with the host traits being signaled, and these profiles should covary; 3) experimental manipulation of scent organ microbiomes should alter organ odor profiles; and 4) doing so should result in altered receiver responses to those manipulated signals. These sorts of investigations are facilitated by current advances in omics technologies, which enable us to determine whether a specific microbial signature associates with a specific behavioral pattern within animal populations and across animal evolution or whether there are holobiont configurations that are favored if there is selective pressure for a certain behavioral trait (Theis et al. 2020).

Climate change

How organisms cope, acclimatize, and adapt in dynamic and changing environments, particularly within the context of global change, is critical to the future of our planet and its organisms. We must understand how host organisms live in association with microbial symbionts and how they will respond individually, together, or through changing associations, adding dimensions of complexity to the identification and study of coevolutionary relationships. Moreover, the biological diversity of phenotypes, genotypes, and organisms, which underlie the potential for differences and possibilities, has not been fully characterized (Pereira et al. 2012). There is a

need to assess how the mismatch in the rates at which microorganisms evolve versus the rates at which macroorganismal hosts evolve and respond to environmental changes, as this influences the condition and performance of holobionts (e.g., Kiers et al. 2010; Correa and Baker 2011; van Oppen et al. 2011). For instance, short-term experiments examining the effects of environmental changes on habitat-forming hosts (e.g., plants, corals, seaweeds) show a link between changes in host-associated microbes in response to environmental stressors (Buerger et al. 2020; Morella et al. 2020; Saha et al. 2020), which then translate into effects on the host. Changes in environmental parameters will be gradual (with the exception of extreme events like heat waves, floods and other anomalies) and may interact in complex ways (Qiu et al. 2019). This timeline may allow for microorganisms to evolve, leading to communities that could be resistant to those changes, potentially influencing holobiont resilience to climate change. Understanding the coevolutionary responses of host and their associated microbes to stressors is critical in order to better predict the effects of environmental changes on holobionts. In turn, this understanding will most effectively leverage microbial ecology to inform conservation efforts.

In the Anthropocene, new diseases and environmental extremes are on the rise (Egan and Gardiner 2016). A grand challenge will be to develop synthetic holobionts with enhanced resistance or resilience to stressors (Damjanovic et al. 2017; Wood et al. 2019). Synthetic holobionts can be of substantial benefit to areas of environmental remediation, restoration, conservation, or crop improvement (e.g., Coleman and Goold 2019). However, our exploration of the ethical issues and ecological implications of synthetic holobionts in the study and trajectories of coevolutionary relationships are in their infancy (e.g., Filbee-Dexter and Smajdor 2019). For example, symbiotic networks of microorganisms can affect the naturalization of invasive species in the introduced region and the ability of these organisms to outcompete native counterparts. Invasion mechanisms employed by some plants involve microbiome shifts between the native and invaded habitats, leading to enhanced resource acquisition and affecting the ability of these plants to outcompete native species (Coats and Rumpo 2014). In ants, symbiont communities can help their hosts by buffering behavioral changes caused by interspecies competition as a consequence of biological invasions (Cheng et al. 2019). These examples substantiate the need to understand the mechanisms underlying the success of invasive holobionts, highlighting the potential implications for conservation biology. Coevolutionary research should enable us to apply what we know to create cleaner solutions to reduce the human footprint on Earth and sustain diversity on our planet.

Glossary. One serious impediment to progress in coevolutionary research is the lack of consistency in the definition of the terms themselves. Since there are ongoing debates on concepts and terminology, we present a glossary with the definitions we are using throughout this manuscript. We call on future authors to state clear definitions that can be used to guide both the design and the interpretation of future research.

Antagonism: An association in which one organism typically benefits at the expense of its partner (e.g., parasitism).

Coevolution: Reciprocal evolutionary change between interacting lineages.

Commensalism: An association in which one partner benefits and other partners are not affected by the interaction. Although it is often difficult to prove empirically that some partners do not gain any net benefit or harm from the relationship.

Facilitation: Species interactions in which at least one species typically benefits from another.

Guild: A group of species that exploit the same resources.

Holobiont: A host and its associated microbiome.

Hologenome: Sum of interacting genomes of the host and its associated microbiome.

Homology: A trait in two organisms that shares common ancestry.

Homoplasy: A trait that has evolved through reversal, parallel or convergent evolution (not by shared common ancestry).

Host: An organism, often multicellular or larger in size in the case of unicellular organisms, that harbors one or more organisms in or on itself.

Interactome: A protein-protein interaction network.

Microbiome: Genetic material of all microbes residing in or on a host.

Mutualism: An association in which all partners typically or predominantly benefit from associating with one another.

Phenotypic plasticity: Adaptive capacity of a genotype to develop different phenotypes in response to environmental variation.

Phylogenetic congruence: Reciprocal corroboration of phylogenetic trees inferred from independent sources of data.

Symbiosis: Intimate association between two or more species. The nature of the predominant outcome of the interaction (positive, neutral, negative) is not a property of the term (i.e. symbiotic does not equate with mutualistic).

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In review

Figure Captions

Figure 1. Spectrum of species interactions range from mutualistic to antagonistic. Mutualistic: plants and their pollinators, such as orchids and orchid bees. Both members benefit from the interaction. Commensal: Barnacles benefit from settling on the whale's skin surface, but do not impact the whale. Competitive: plants competing for access to canopy light in a forest. Antagonistic: The cuckoo lays its egg in the nest of another species of (host) bird. The host bird incurs the cost of raising the cuckoo's young instead of its own (which the cuckoo hatchling destroys).

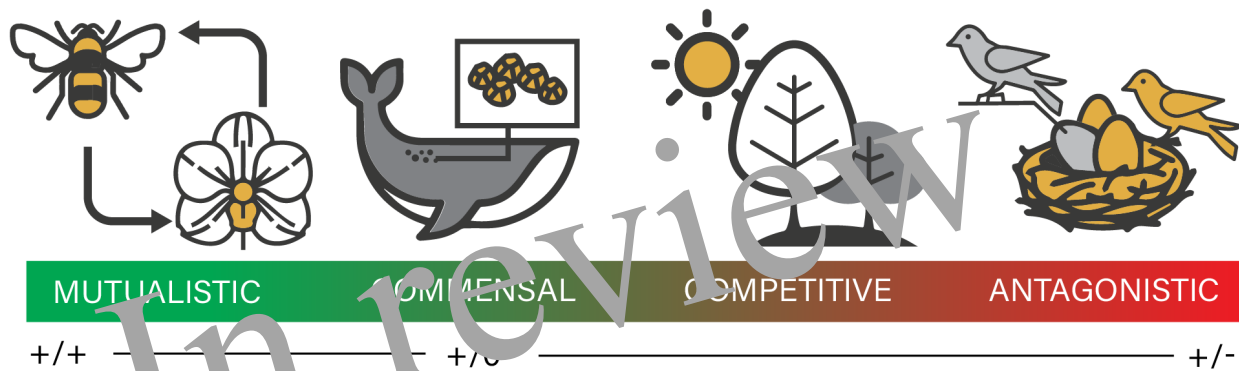


Figure 2. Coevolutionary networks, such as the vertebrates, invertebrates, plants and microorganisms that interact with tomato plants (*Solanum* spp.), result in species interactions with different levels of codependency. 1: common rust fungus can infect the tomato plant, leading to leaf mortality; 2: a wasp caterpillar parasite; 3: Arbuscular mycorrhizal fungi (AMF) are plant symbionts; 4: invertebrates and microorganisms such as nematodes and bacteria can have detrimental effects on plant roots; 5: other plant species can compete with *Solanum* for nutrients and space crop fields; 6: frugivores benefit from consuming tomato fruits and disperse seeds; and 7: pollinators such as bees contribute to the plants reproductive output. 0 = neutral interaction, $+$ = beneficial, $-$ = detrimental.

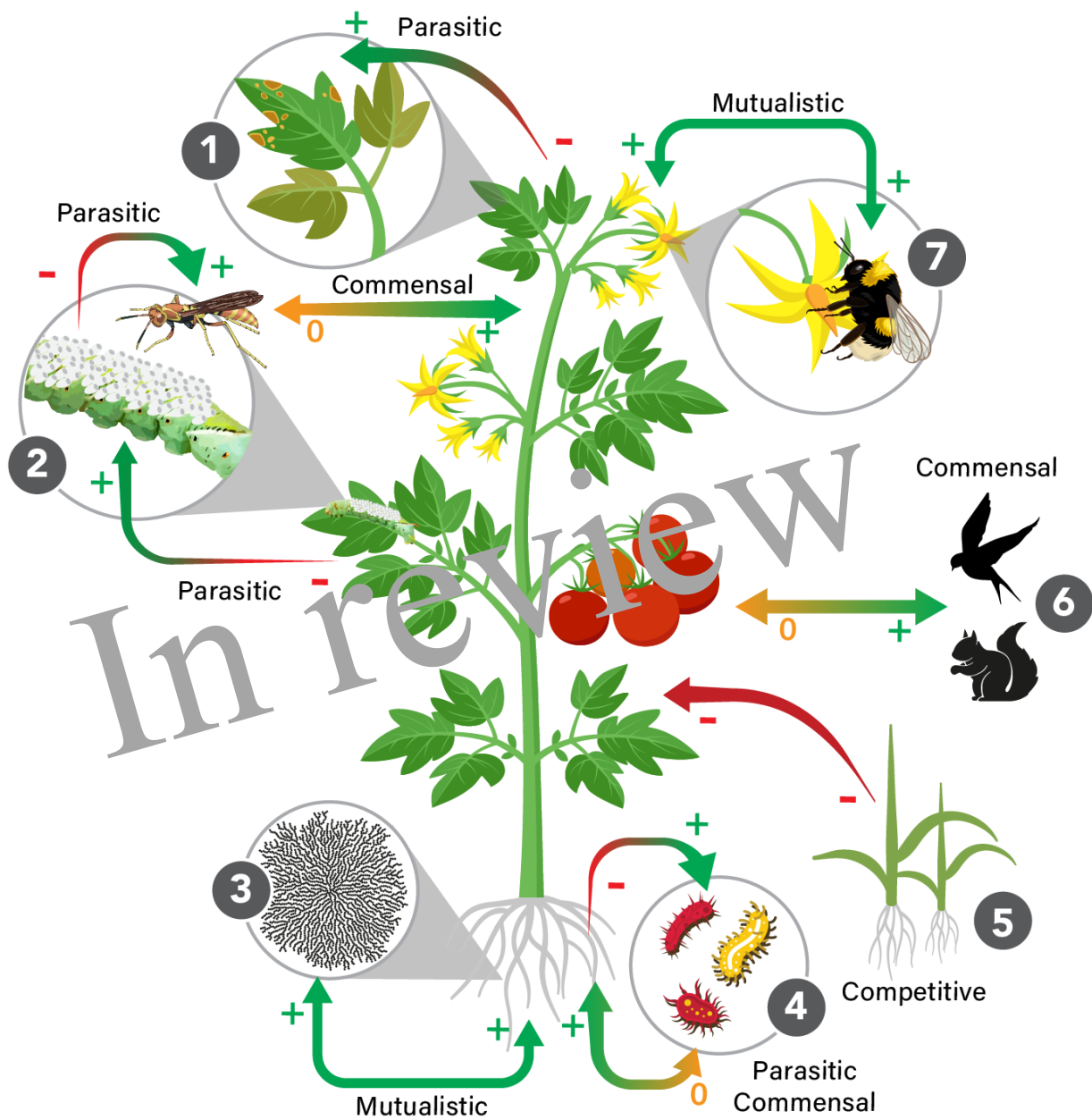


Figure 1.JPEG

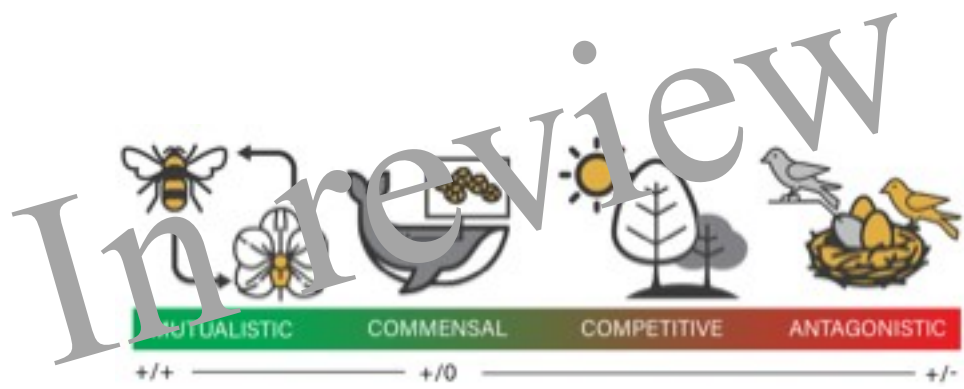


Figure 2.JPEG

