The co-evolutionary genetics of ecological communities

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Abstract | Co-evolution has produced many intriguing adaptations and made significant contributions to biodiversity through the co-adaptive radiations of interacting groups, such as pollinating insects and flowering plants or hosts and endosymbionts. New methods from molecular genetics and comparative genomics, in conjunction with advances in evolutionary genetic theory, are for the first time providing tools for detecting, investigating and understanding the genetic bases of the co-adaptive process and co-speciation. Advances in the emerging field of community genetics, which integrates genetics and community ecology, could revolutionize how co-evolution is studied, how genes are functionally annotated and how conservation geneticists implement preservation strategies.

Geographic mosaic
A theory of community ecology that was founded on the premise that communities are genetically and ecologically subdivided so that the rate of co-evolution varies geographically, resulting in rapid co-evolution (hot spots) in some localities but slower co-evolution (cold spots) in others.

Congeners
Species that are members of the same genus.

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Darwin[1] recognized that ecological interactions among species are the most important processes that drive the adaptive evolution and diversification of species: "I can understand how a flower and a bee might slowly become, either simultaneously or one after the other, modified and adapted in the most perfect manner to each other, by continued preservation of individuals presenting mutual and slightly favourable deviations of structure." Patterns of co-adaptation result from the process of co-evolution, which occurs whenever two ecologically interacting species exert reciprocal selection pressures on one another and the response is inherited. Although most interactions between species, including those between competitors, predator and prey, host and parasite, or host and symbiont, generate reciprocal selection pressures, the specific pattern that emerges over time varies with the nature of the ecological interaction, the genetic architecture of the co-evolving traits and the degree of co-transmission across generations. The degree of co-transmission alters the predictions and outcomes of the standard co-evolutionary models that assume random mixing of species.

Despite the central importance of ecological interactions among species for Darwinian natural selection, the formal study of the evolutionary genetics of ecological interactions began relatively recently[2–4]. Many of the central research questions of today are much the same as those that were identified in earlier research: Does co-evolution lead to highly specialized adaptations with particular partners, or is it diffuse, involving general adaptations for successful interaction with many other community members? Does it promote co-existence, resulting in stable and more diverse ecological communities? Does it lead to the functional integration of ecological communities, so that the loss of one species endangers the whole community? Does the microevolutionary process of reciprocal co-evolution lead to a geographic mosaic pattern of hot spots and cold spots of co-adaptation? And, is this a necessary intermediate to a macroevolutionary pattern of co-speciation?

Recently, ecological studies of adaptation have begun to merge with comparative molecular phylogenetics. New species of endosymbionts have been revealed by probing putative hosts with bacteria-specific 16S rRNA sequence[5], allowing the discovery of cryptic co-speciation between interacting clades and placing co-evolutionary questions in an historical context. With the growing availability of genomic data, newer questions that are uniquely genetic are being posed: What are the relative rates of co-evolution of hosts and their parasites? Do endosymbionts evolve faster than their free-living congeners? Is gene loss from parasite genomes the result of positive selection for rapid replication, or relaxed selective constraint and the fixation of deleterious mutations owing to smaller effective population size? Do the same processes that govern gene loss also favour gene transfer from symbiont to host genome?

In this Review, I summarize the progress that has been made so far and point out the gaps that remain in our understanding of co-evolutionary genetics. I begin by discussing patterns of co-adaptation and co-speciation to illustrate the consequences of co-evolution for populations and communities. Next, I

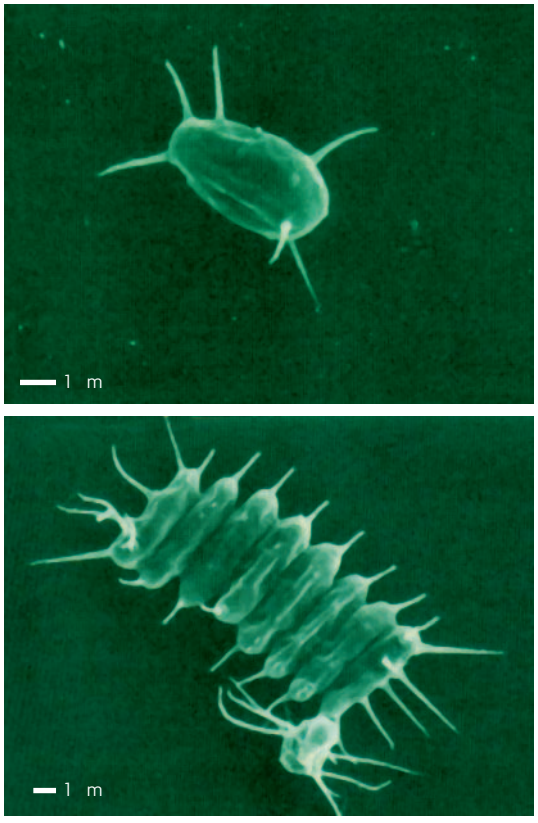


Figure 1 | **Example of an inducible defence in phytoplankton.** Grazing by the herbivorous water flea *Daphnia magna* induces colony formation in *Scenedesmus subspicatus* (shown above), and the development of additional spines in other phytoplankton of the genus *Scenedesmus*. Reproduced with permission from REF. 64 © (1993) Schweizerbart Verlag.

review why concepts from evolutionary genetics theory such as genotype-by-environment interaction (G x E), epistasis (G x G) and population genetic subdivision become especially important in investigations of co-evolution. I also examine why genetic variation in the effect of one species on another requires changing the genetic (G), environmental (E) and interaction (G x E) components of the standard nature–nurture paradigm, focusing more attention on the higher-order interactions (G x G x E) that define the geographic mosaic[3]. Next, I review the new concept of intergenomic epistasis, wherein genes of one species interact with specific genes in another, and how community structures that allow co-dispersal or co-transmission of genes and pathogens allow a response to natural selection that directly influences these interspecific gene combinations. I show how the co-inheritance of *trans*-specific gene combinations can be estimated using a parameter that was devised to measure epistasis between genes within the same genome. Finally, I argue that community genetics, which integrates genetics and community ecology, is the most likely field to unify the life sciences. Community genetics revolutionizes the way genes are functionally annotated, because the genes that cause a phenotype in one species can reside in the genome of another, and because it adds co-dispersal as an important feature of the preservation of endangered species and ecosystems.

Examples of reciprocal co-evolution

Morphological, biochemical and behavioural defences are examples of an adaptation in one species that results from selection pressures that are generated by another species. Although many defences and the genes that code for them are constitutively expressed, some are expressed only when they are cued by certain ecological contexts, like the density-dependent expression of quorum sensing genes of some bacteria[6]. Many prey species have phenotypically plastic morphologies that respond to gene expression changes that are induced by cues associated with predators. These inducible defences are manifest only in the presence of predators because building elaborate defences that take resources away from growth and reproduction is costly[7]. Inducible defences range from the protective spines of the water flea *Daphnia pulex*, which thwart predation by fly larvae[8] in the genus *Chaoborus*, to changes in the shell morphology of the acorn barnacle, *Chthamalus anisopoma*, which reduce predation by specialized gastropods[9]. *Daphnia* spp. not only have inducible defences, but also induce defences in their prey. Grazing by *Daphnia magna* on algae in the genus *Scenedesmus* triggers a change from single-cell growth to colony formation and the production of more and longer spines (FIG. 1); these changes in algal colony morphology have been shown to reduce grazing by more than half[10–12]. By reducing prey vulnerability, inducible defences alter the trophic structure of ecological communities[13].

In a host–pathogen interaction, variation from one host individual to another in the numbers or virulence of pathogens causes differences among hosts in viability and fecundity. As a result, hosts that are better able to avoid contact with the pathogen or resist infection live longer and leave more offspring than those that are more susceptible. If the hosts also vary genetically in these traits, mean avoidance and mean resistance increase in the host population as a result of the selection pressure that is exerted by the pathogen. Reciprocally, variation from one pathogen to another in the ability to find or infect resistant hosts causes differences among pathogens in viability and fecundity. As a result, those that are better able to find and infect hosts will leave more offspring than those that are less competent. If the pathogens vary genetically in these traits, mean pathogen fitness will increase as a result of the selection pressure on its population that is exerted by resistance in the host species. If the hosts and pathogens mix randomly at each generation, the net result is a co-evolutionary arms race, wherein both mean host resistance and mean pathogen infectivity increase over time, increasing the risk of extinction of one or the other species. This simple co-adaptive scenario can be significantly altered if hosts are co-infected with multiple genetic strains of parasites. In this case, competitive growth of pathogen strains within

Quorum sensing
Gene expression patterns in bacteria that are conditional on colony density.

Inducible defence
An adaptive phenotypic change in a prey species that develops in response to predation on conspecifics, which reduces vulnerability.

Trophic structure
The species interactions that make up food chains and energy flows through an ecological community.

Co-evolutionary arms race
The escalating and reciprocal co-evolution between the offensive ability of a predator and the defensive capability of its prey.

individual hosts might or might not constitute a life-history trade-off with finding susceptible hosts, depending on the direction of within-host selection and the genetic architecture of the pathogen traits.

By contrast, co-evolution between species that compete for the same resource can lead to diminished competitive interaction and co-existence. In this case, both individuals vary in their ability to find and consume a common resource. In one species, those individuals that are better able to utilize resources that are different from those utilized by the competitor experience less competition and have higher fitness than those with a resource utilization that more extensively overlaps that of the competitor. Given genetic variation in resource utilization traits in each species, mean resource usage diverges between them, a phenomenon called character displacement, and the ecological interaction between them weakens over time. In both cases, co-evolution affects the structure of an ecological community by affecting the intensity of interactions among its members.

Although we expect adaptive natural selection to lead to an increase in the population size of a species[14], this tendency is opposed by the adaptation of other species in an ecological community, especially competitors, predators, pathogens and parasites. This relentless deterioration of the ecological environment that is caused by adaptation in other species, the Red Queen hypothesis[14–16], was first described by Darwin[1]: "…if any one species does not become modified and improved in a corresponding degree with its competitors, it will soon be exterminated."

Whenever mean fitness depends on the environment, adaptation by natural selection can lead to Darwinian extinction[17]. Because natural selection works on differences in relative fitness within populations, it is possible for mean population fitness to decline to zero (which is synonymous with extinction), even when traits that confer higher relative fitness within a population are favoured. Whenever there are interactions between species, the positive association between the individual and the population mean fitness that is anticipated by R. A. Fisher[14] can be mitigated or reversed. For example, the well-known population oscillations that result from predator–prey interactions are intensified if natural selection increases predator attack rates, thereby increasing the risk of extinction for both species[17]. Extinctions are a relatively common feature of evolutionary models of predator–prey and host–pathogen interactions, as well as competitive interactions. Interestingly, mutualistic interactions are not subject to Darwinian extinction because of the positive feedback between increasing individual fitness and increasing population density of both participants[17]. Extinction of interactions with negative feedback and preservation of those with positive feedback constitute an 'ecological sieve' that enriches a community with mutualistic interdependent species, enhancing its diversity and stability. If true, these communities should differ markedly from the stochastic assemblages that are predicted by neutral community theory[18].

Life-history trade-off
A negative correlation between viability and the amount or timing of reproduction, such that an increase in one results in a concomitant decrease in the other.

Character displacement
Phenotypic differences between sympatric species that arise as an evolutionary response to competition for shared, limiting resources.

Red Queen hypothesis
The continual evolutionary change by a species that is necessary to retain its place in an ecosystem because of ongoing co-evolution by other species.

Darwinian extinction
A decline in mean fitness that occurs as a result of adaptation by natural selection, which reduces the size of the population until it becomes inviable.

Gene-for-gene model
A model of host–pathogen co-evolution that proposes that, for every gene in the host that confers resistance, there is a corresponding virulence gene in the pathogen.

Genotype-matching model
An ecological genetic model of host–pathogen co-evolution that proposes that rare host genotypes escape the more abundant pathogens, which are adapted to more common host genotypes, leading to oscillations in population size and genetic composition of both species.

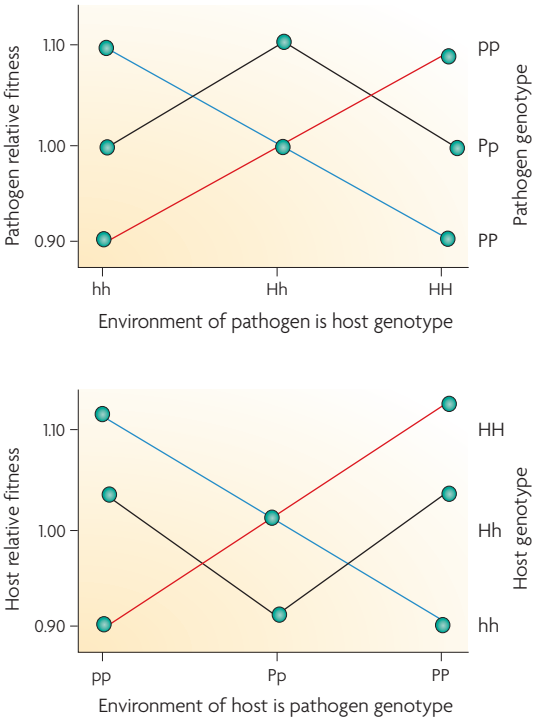
Co-evolutionary genetics

Ecology and evolutionary genetics have long been separated by the argument that gradualistic Darwinian evolution occurs on a timescale that is much slower than that of more rapid ecological processes, like succession. This argument allows ecological theory to treat individuals as genetically uniform, unchanging and interchangeable, and allows evolutionary genetics to ignore the ecological consequences of adaptation that might affect individual relative fitnesses or population mean fitness. The discovery that strong selection is common and that measurable phenotypic responses can occur over a handful of generations have undermined this barrier assumption[19–21]. Furthermore, evolutionary theory in the mid-1980s established that co-evolution, strictly speaking, does not take place between two species, but rather between the traits of two (or more) species[22–23]. These theoretical advances and the innovations in molecular evolutionary methods now allow the identification of the genes that are involved in both members of ecologically interacting species and the direct study of the genetic basis of reciprocal co-evolution. Genes that are expressed in individual genomes have been shown to have a pronounced effect on the structure of ecological communities[19]. The outcome of natural selection working on a population of a particular species can depend on the standing genetic variation in a population of a different species[21]. These interspecific interactions change the standard genotype-by-environment (G x E) interactions into the G x G x E models that Thompson[3] used to define the geographic mosaic of co-evolution and introduce the novel concept of interspecific epistasis[21] into co-evolutionary theory.

Host–pathogen systems are one of the most promising for studying interactions between genes in two ecologically interacting species. Over the past two decades, quantitative- and statistical-genetic methods have revealed the existence of a tremendous amount of genetic diversity among host individuals for pathogen resistance, and a matching genetic diversity in pathogens for overcoming these host defences[24]. Furthermore, molecular evolutionary genetic studies have shown that genes in host immune systems are some of the most rapidly evolving genes. Explicit genetic theories of co-evolution, such as gene-for-gene and genotype-matching models, have been developed to explain both the genetic diversity and the rapid sequence evolution[25]. These models and their effects can be viewed through the lens of genotype-by-environment (G x E) interactions (BOX 1). G x E theory captures an essential feature of the evolutionary genetic trade-offs that are experienced by host and pathogen: the genotype with the highest fitness in one environment does not have the highest fitness in another environment. Such genetic trade-offs can maintain a high level of genetic diversity within a population when individuals disperse between environments and between generations. The evolutionary engineering problem that is posed by G x E can be solved by adaptive plasticity — the ability of an organism to change its growth form and thereby increase its fitness in response to environmental cues[7–13,26–30].

Box 1 | **G x E in the co-evolution of hosts and pathogens**

As the environment changes, the phenotypes that are produced by one genotype can also be altered. The changing map of genotype to phenotype is called a 'norm of reaction'[29], and is depicted as a line on a graph of phenotype (*y*-axis) versus environment (*x*-axis). For a set of genotypes, the genotype-by-environment interaction (G x E) is a change in the magnitude or order of their phenotypes as a result of changes in the environment. When several norms of reaction are plotted on the same graph, G x E is evident as changes in the scale or order of the genotypes across different environments. When fitness is the phenotype, a change in scale means that the rate of evolution is different in different environments, because the variance in fitness among genotypes differs among environments[14]. The other type of G x E, a change in the order of the genotypic fitnesses (visually, the crossing of reaction norms as depicted here), means that altering the environment changes the genetic outcome of evolution: the fittest genotype in one environment is not the fittest in another. This kind of G x E promotes the maintenance of genetic diversity within populations[31], and occurs when different members of the same population experience different environments. In host–pathogen interactions with a matching of genotypes across species, in some genotypic combinations the host has high fitness but the pathogen has low fitness (for example, HH and PP), whereas in other combinations the fitness relationships are reversed (for example, hh and PP). When host and pathogen genotypes are randomly mixed between generations, these types of co-evolutionary interactions maintain genetic diversity in both species, functioning as a constraint against the selective loss of genetic variation (that is, G x E is an evolutionary constraint that slows evolution[26–31]). However, if mixing across environments is diminished or halted entirely, the constraint is removed and the evolutionary genetic response to selection accelerates[39–40]. When host genes and pathogens are co-transmitted to host offspring, mixing is prevented and G x E becomes Thompson's G x G x E[3]. Furthermore, selection can directly influence host–pathogen gene combinations (interspecific epistasis) when rates of co-transmission are high.



The evolution of inducible defences and G x E. Inducible defences are a textbook example of adaptive plasticity, which is believed to be an evolutionary response to G x E[27–30] (BOX 1), wherein some genotypes have higher fitness than other genotypes in one environment but lowered fitness compared with others in another environment. However, in the standard treatment of G x E, the environmental variation is abiotic and does not have a genetic component. As a result, the species evolves but the environmental context does not. In this case, adaptive plasticity maximizes fitness across a fixed distribution of environmental contexts.

Co-evolution is different because the relevant contexts are other species with evolving genes (BOX 1). In this case, the evolutionary fate of a gene depends not only on the context it experiences, but also on the evolutionary trajectory of that context. For an herbivorous species, its plant resources, as well as its predators, symbionts and parasites, all contain genes. Furthermore, the ecological context of these other species is often associated with large fitness effects. The reciprocal co-evolution of one species in response to the genetic context of another is integral to the process of co-adaptation between species, and is believed to contribute to the functional integration of ecological communities and maintenance of biodiversity[3].

There are several ways in which the ecological community can affect genotypic fitnesses in a particular species[20]. All members of a focal species can experience the same average community[22] if member species are well mixed within and between generations. Unless heterozygous genotypes have the highest fitness, this kind of homogenous experience of community context does not favour genetic diversity in the focal species. However, different genotypes of the focal species might experience different ecological contexts, as occurs when genotypes have different habitat preferences and distribute themselves non-randomly within the community[30]. Conversely, other members of the community might associate non-randomly with genotypes of the focal species[19–20]. In either case, there is a co-variation between genotype and evolving context, which can either increase or decrease the variance in fitness and therefore the rate of co-evolution. These are the circumstances under which G x E promotes the maintenance of genetic diversity in the populations of a community[31] and the evolution of adaptive phenotypic plasticity[29]. Finally, when natural selection favours particular genotype combinations of two species, the level of co-inheritance of genes across species determines whether co-evolution will lead to conflict or cooperation.

These considerations have led to the recent confluence of genetics and ecology resulting in the birth of a new field, community genetics[19–21]. It addresses the genetics of co-adaptation between and among species in an ecological community, with the goal of understanding the functional organization of biological communities. In standard community ecology, it is assumed that ecological and evolutionary processes are separated in practice by a large difference in timescale, with demographic and ecological processes achieving equilibria much more rapidly than gradualist evolutionary forces. However, strong selection frequently violates

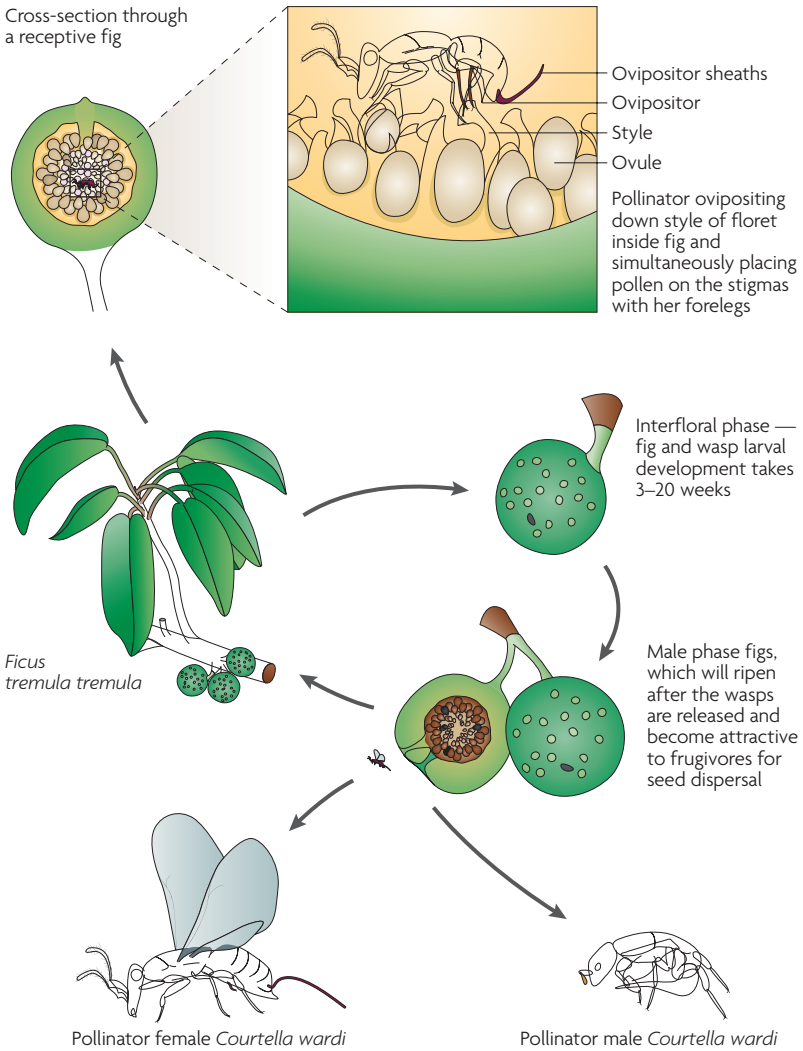


Figure 2 | **Co-evolutionary mutualism of figs and fig wasps.** Fig trees of the genus *Ficus* have an enclosed inflorescence on the side of the fruit. Pollination is effected by species-specific pollinating female wasps in the family *Agaonidae*, such as *Courtella wardi*. Pollinator females enter the fig (losing their wings and antennae in the process), pollinate the flowers and rear their own progeny — one wasp in each seed, in a subset of the seeds. Pollinator males, after mating with females, chew an exit hole through the fig wall, allowing pollen-laden females to escape from the fig cavity. On leaving the natal figs, pollinator females home in on volatiles that are released by receptive figs on other trees. This is an obligate mutualism in which both species are completely interdependent on one another[33–34]. Reproduced with permission from the Figweb web site © (2004–2007) Figweb.

the assumption of disparate timescales for ecological and evolutionary processes. Empirical evidence shows that genetic variation, especially in keystone species, can have important consequences for local communities and entire ecosystems[3,19–21]. Keystone species are dominant in function and structure in an ecosystem. They can be crucial to its integrity and, consequently, affect the survival and abundance of many other species. If it can be shown that genetic diversity in one species commonly affects biodiversity in the rest of the community, it will revolutionize the conceptual foundations of conservation biology, environmental policy and forest and wetland management.

Gene flow
The movement of genes from one population to another, as individuals leave their population of birth and become breeding members of another.

Studying co-evolutionary relationships

Co-evolution and macroevolution. Molecular phylogenies of clades to which two interacting species belong provide an historical context for the study of co-adaptation[4,32], by allowing reconstruction of ancestral environments for both interactants. Using sequences from a panel of host species and a comparable panel of parasite species to build gene trees, concordance between phylogenies can be estimated from the similarity of the branching patterns across the two clades. This is often taken as evidence for co-speciation. Because microevolutionary processes of co-evolution occur between genes and not between species, it is likely that such studies miss a great deal of co-evolutionary adaptation. Nevertheless, this kind of data can address questions about the relative rates of co-evolution, in terms of rates of base pair substitutions, in genes that are not intimately involved in co-adaptation. Reciprocal phylogenetic data can show how long it takes to establish an obligate relationship between a species pair or to evolve a new phenotype. Clearly, long-term intimate associations between species provide ample opportunity for reciprocal fitness effects and the co-adaptations that they foster, as exemplified by figs and fig wasps[33–34] (FIG. 2). However, it is an open question whether such co-adaptation is a cause or a consequence of speciation.

The phylogenetic trees of feather lice and bird hosts[4] (FIG. 3a), and of aphids and bacterial endosymbionts, (FIG. 3b) are similar[35]. However, the expected degree of phylogenetic concordance is affected by biogeographical events, such as parasite speciation (duplication) within a host or host-switching events by parasites, that are independent of the microevolutionary process of co-adaptation[36]. Given the difficulties that gene duplication and gene loss pose for the congruence of gene trees within species, it is not surprising that congruence between clades of different taxa is difficult to sustain, especially when there is a possibility of host switching.

Although phylogenetic congruence is imperfect for many types of ecological associations[32,36], the strong concordance between the phylogenies of maternally inherited intracellular bacteria and that of their aphid hosts indicates a special context in which co-adaptation and co-speciation go hand in hand. In this case, the parallel pathways of host gene transmission and host associate transmission from one generation to the next (see below) present ideal conditions for the co-evolution of reciprocal obligate symbioses and their co-speciation. The high level of co-inheritance of genes across species guides the co-evolutionary process away from conflict and towards cooperation.

Co-evolution and meta-communities. When ecological communities are geographically subdivided, they are called meta-communities. Geographical variation in the amount of gene flow between local communities causes genetic differences among populations of the component species and modulates the rate of co-evolution[3]. The degree of local genetic differentiation can be measured for each member species in a community using standard measures of genetic distance,

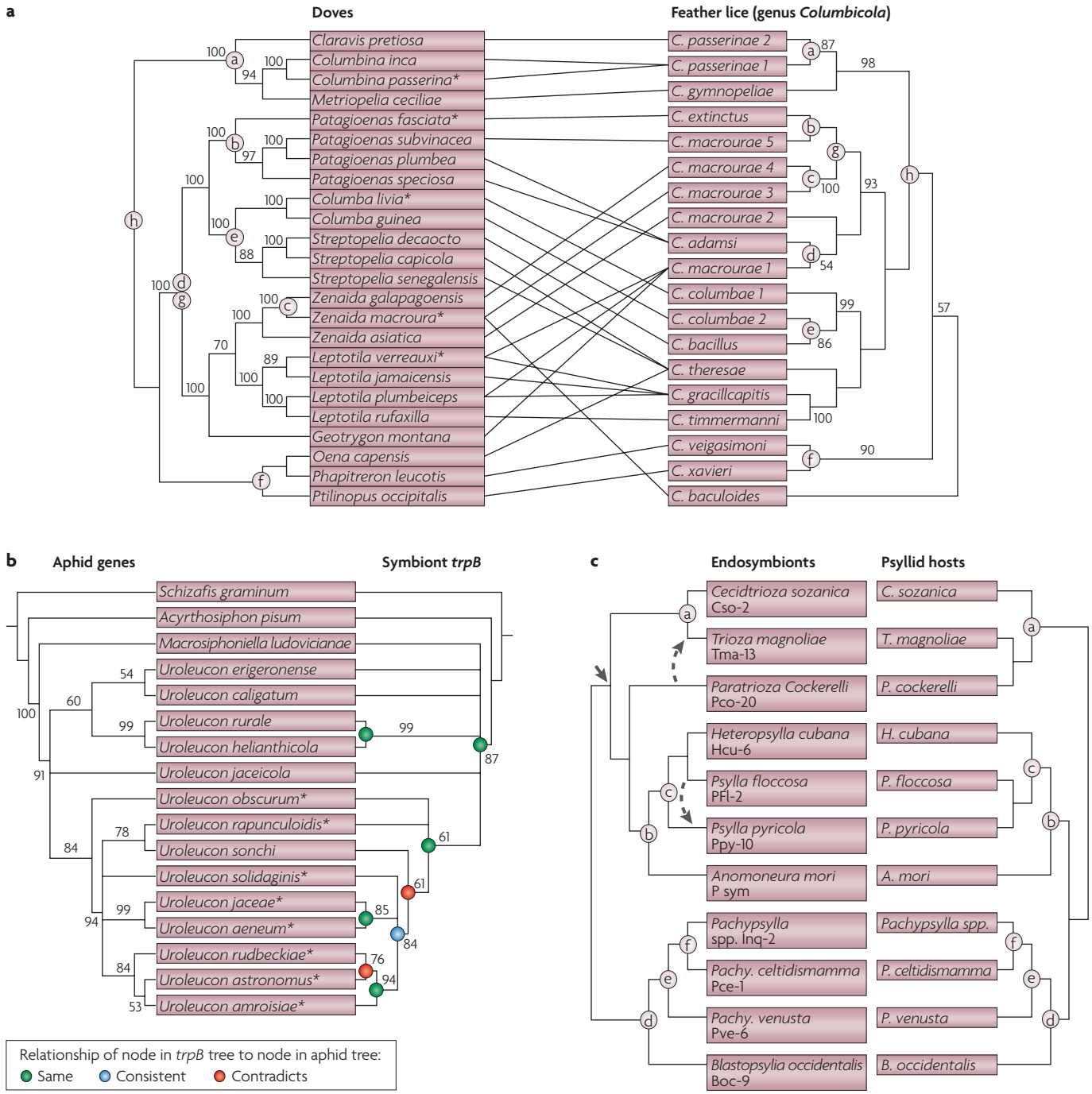


Figure 3 | **Examples of tangled phylogenetic trees and co-speciation. a** | Phylogenies of doves and their feather lice in the genus *Columbicola* are shown, indicating examples of co-speciation (denoted by circles with letters), duplication and host switching. Numbers after the species names of lice indicate cryptic species, numbers beside tree branches give the percentage of maximum likelihood bootstrap replicates, and asterisks indicate species that have been used in experimental studies. Host defences reinforce the co-speciation process by reducing the frequency of host switching[63]. **b** | Gene trees for aphids and their *Buchnera* bacterial endosymbionts represent one of the clearest patterns of co-speciation. The bacterial endosymbionts synthesize amino acids that are essential to their phloem-feeding aphid hosts, which have a diet that is rich in carbohydrates but otherwise nutritionally poor. This association is estimated to be 100–200 million years old[35]. **c** | A maximum likelihood gene tree of endosymbionts (clone names below species names) is shown, which was constructed using 16S rDNA in relation to a morphology-based tree of their psyllid hosts. Circles with letters indicate congruence between host and endosymbiont branching. Arrows indicate incongruence owing to placement of the host tree root (black arrow) and two host taxa (dashed arrows). *trpB*, tryptophan B. Panel **a** is reproduced with permission from REF. 63 © (2003) National Academy of Sciences. Panel **b** is reproduced with permission from REF. 35 © (2000) Blackwell Scientific. Panel **c** is reproduced with permission from REF. 65 © (2001) Blackwell Scientific.

such as Wright's F_{ST} (REF. 37), which measures the fraction of the total genetic variation among communities as opposed to that within communities. Different species in a community will often have different rates of dispersal and vary considerably in measures of genetic distance. However, spatial genetic variation in either member of a species pair can result in local co-adaptation being rapid (hot spots) in some places but slow elsewhere owing to selective constraints (cold spots)[3,38].

In many cases, the degree of genetic divergence among communities will be similar for different species. For example, restricting gene flow among host populations is tantamount to restricting gene flow among the endoparasite populations of that host. With interspecific G x E (BOX 1), the cessation of gene flow removes selective constraints and allows more rapid, diversifying evolution in both species[39–40]. Therefore, the genetic architecture of the interspecific interaction is one factor that contributes to local variation in the extent of co-adaptation. This leads to a pattern of interspersed hot spots and cold spots of co-adaptation, which Thompson calls the geographic mosaic[3,32,38]. Because genetic isolation with G x E can lead to rapid adaptive divergence, it is also reasonable to infer that it might contribute causally to the macropattern of co-speciation in some types of ecological interactions. Whenever the activities of one species directly affect gene flow in another, as in the case of the pollinating activities of fig wasps for figs[33–34], the inference becomes stronger.

Gene interactions across genomes. Population genetic theory that was developed to understand the evolution of gene interactions (epistasis) that underlie complex traits[41–43] has recently been applied to host and symbiont co-evolution[44]. Epistasis describes the situation in which a phenotype is determined by the interaction of two or more genes. In physiological genetics, the interaction is biochemical, whereas in evolutionary genetics, the interaction is statistical[45–47]. For example, mitochondrial-gene interactions with nuclear genes are well studied from a physiological genetic viewpoint, but mitochondrial–nuclear epistasis has received much less attention from statistical genetics. The role of gene interactions in evolution is difficult to understand because adaptive gene combinations are not transmitted directly from parents to offspring. If some individuals of a species have high fitness because of specific gene combinations, recombination and random mating during reproduction scramble and remix the genes, often destroying specific high-fitness gene combinations in the process. There is a tension between natural selection increasing the frequency of a particular combination and transmission breaking it up. Its evolutionary outcome depends crucially on the degree to which its component genes are co-inherited. It is for this reason that epistasis, like G x E, is considered a constraint on adaptive evolution[39]. In other words, recombination moves a gene from one genetic background to another and, with epistasis, the gene is selectively favoured in certain genetic backgrounds but not in others. The average selection that is experienced by the gene is weaker than it would be if the gene were favoured in every individual on all genetic backgrounds. It is this weakening of selection (relaxed constraint) by both epistasis and G x E that allows complex genetic diseases to be so prevalent in the human population.

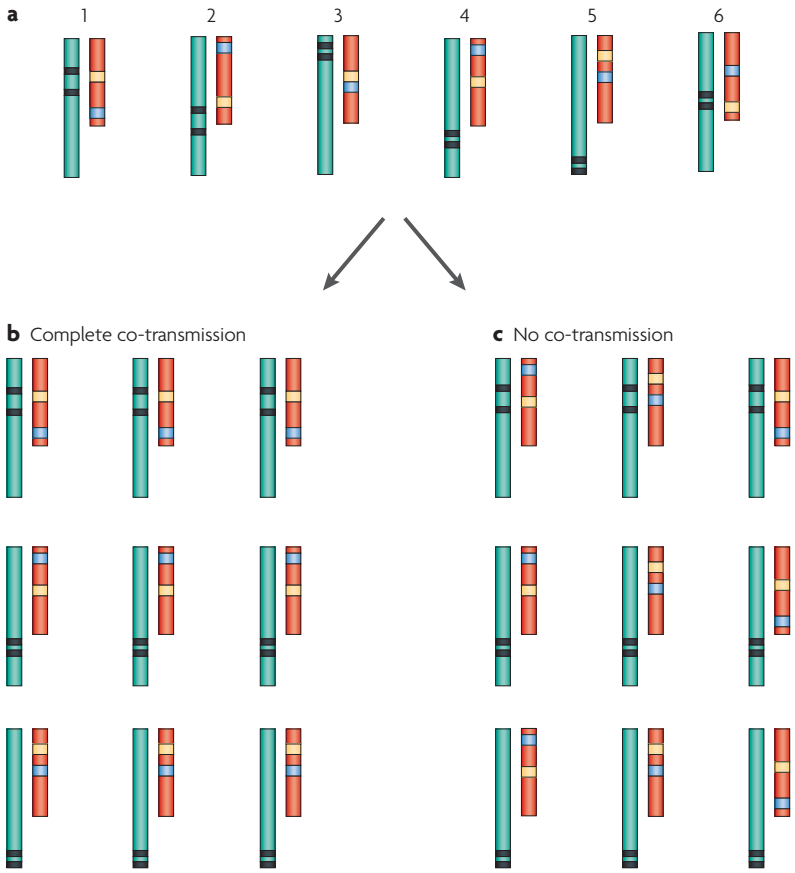
However, recombination varies with chromosomal position, sex, temperature, age and mate number[48], and population genetic structure prevents complete random mating and mixing of genes across an entire species[42]. So, some conditions, such as inbreeding and population genetic structure, favour the co-inheritance of gene combinations, whereas others do not[44]. The parameter Θ measures the degree of co-inheritance of gene combinations[41–44]. When Θ is high, as in the case of gene combinations (regardless of the mating system) that are in regions of reduced recombination (for example, genes on the same inversion or in the mitochondrial genome), then they are co-inherited with properties that are similar to those of single genes. When Θ is low, as in the case of unlinked genes in large, randomly mating populations, then gene combinations have little if any heritability and selection on them must be strong for any adaptive progress to occur. The maintenance of synteny of genes over long evolutionary time periods is indicative of the evolutionary importance of epistasis and high Θ.

To estimate Θ between two genes in the same genome, one needs a sample of both genes from individuals of known relatedness across two generations. From each individual, DNA from regions in or near each gene that is known to be variable is amplified and sequenced. The gene sequences from each individual remain paired for analysis to determine the extent to which knowledge of one gene variant is predictive of the other. This can be estimated using well-known statistical methods for estimating the degree of association between pairs of genes[49]. Fortunately, most mechanisms of co-dispersal and co-transmission involve whole genomes, so that high values of Θ between two genes imply high values between many genes (see the example below).

The role of horizontal transmission of parasites and symbionts among hosts in co-adaptation between species is similar to the role of recombination in the co-inheritance of gene combinations within species. Co-inheritance of gene combinations across species can also be measured by the parameter Θ, if it is redefined as the simultaneous co-variance in identity-by-descent of host and symbiont genes when two infected hosts are compared. High levels of horizontal transmission diminish Θ, whereas low levels enhance it (BOX 2). With purely horizontal transmission, Θ is low; the genetic response of hosts to the selection that is imposed by variations in the virulence of their parasites is independent of the genetic response of parasites to the selection that is imposed by variations in resistance among hosts. The result is an interspecific arms race with each species independently pursuing its own evolutionary optimum.

Synteny
The conservation of gene order over chromosome segments across taxa.

Box 2 | **Using gene sequences to study co-inheritance of parasites on hosts**



The co-inheritance of gene combinations is measured by the parameter Θ, which represents the simultaneous co-variance in identity-by-descent of host and symbiont genes when two infected hosts are compared. The vertical transmission of a parasite from mother to offspring is similar to the maternal inheritance of mitochondria that occurs in many animals and plants. Vertical transmission can be intracellular, as in the aphid–*Buchnera* system[35], interstitial, as in the fungus–*Danthonia* symbiosis[62], or social, as might occur in birds and mammals with intimate postnatal contact between mothers and developing young[4,63]. In the case of vertical transmission, if the mitochondrial genes of two infected individuals are identical-by-descent, so are the genes in their symbionts or parasites. This leads to high values of Θ, which are indicative of co-transmission, and to direct and efficient natural selection on the gene combinations that are involved in the host–symbiont or host–pathogen interaction, even though the genes reside in two different genomes. In the case of horizontal transmission of the parasite, even if the mitochondrial genes of two infected individuals are identical-by-descent, identity-by-descent is unlikely for the genes of their parasites.

The level of co-inheritance can be estimated with a collection of infected hosts, such as the six infected hosts in panel **a** or the nine infected hosts in panels **b**,**c**. Each host and its associated parasite are genotyped using variable molecular genetic markers (host genes are indicated in green with variable markers in black, and parasite genes are indicated in red with variable markers in yellow and blue). The host–parasite pairs in panel **a** are the parents of the offspring host–parasite pairs in panels **b**,**c**. Some host parents from panel **a** (numbers 1, 2, and 4) have each produced three offspring, whereas the other three parents have produced none. With a high level of co-inheritance, as in panel **b**, particular parasite genotypes will be clustered according to host genotype. Conversely, without co-inheritance, as in panel **c**, there will be no detectable association between host and parasite genotypes. The degree of co-inheritance in natural populations will lie between the two extremes that are depicted here, and well established statistical methods (for example, REF. 49) can be used to estimate the magnitude of the association between host and parasite genotypes.

Even the intimate symbiosis between mitochondrial and nuclear genes is affected when Θ is low, as it can be in large, randomly mating, diploid populations[44]. Effective population size of mitochondrial genes is one-quarter that of nuclear genes, because the mitochondrial genome is haploid and inherited only through females in most organisms. Consequently, mitochondrial variants become fixed in populations by random genetic drift more rapidly than do nuclear variants. This chance fixation has its own consequences for adaptive evolution when there is epistasis between cytoplasmic and nuclear genes. Random genetic drift converts epistatic to additive nuclear variation, in the same way that holding one of two interacting factors constant in a replicated experiment converts the factor interaction into main effects for the remaining variable factor. When one genome experiences stronger drift than the other, there is a bias in the conversion of epistatic to additive variance. In this case, the bias favours the creation of additive nuclear variation, which is the kind that is useful for an adaptive response to natural selection[44]. So, for such cyto-nuclear gene combinations, mutation and drift govern evolution of the mitochondrial genes, whereas natural selection governs evolution of the nuclear genes. In co-evolution, random genetic drift in a two-species system is governed by the species with the smaller effective population size in an analogous way[22].

Vertical transmission of parasites from parent(s) to offspring is not only analogous to genetic transmission, but it formally increases Θ. With high levels of vertical transmission, two interacting genomes are inherited as one and genomic conflict between them is necessarily mitigated[44]. Whether interacting combinations of host and pathogen genes are transmitted together or independently ultimately determines whether an interspecies interaction evolves as a co-evolutionary arms race, whereby host resistance and pathogen virulence increase together, or as a more intimate, reciprocal symbiosis, whereby host and symbiont are obligately genetically associated.

To estimate the parameter Θ in these co-evolutionary cases, one needs a sample of infected hosts from two generations (BOX 2; FIG. 1). From each host individual, DNA from regions that are known to be highly variable is amplified and sequenced, as is DNA from the parasite(s) infecting each host individual. Then, host and parasite samples are paired for analysis to determine the extent to which knowledge of the host variant is predictive of the parasite variant. This can be estimated using any of the methods for estimating associations between pairs of genes[49].

Interspecific G x E and epistasis. The host–pathogen genotype combinations in BOX 1, which are used to illustrate G x E, can also be interpreted as intergenomic epistasis, whereby a parasite gene against the genetic background of one host has a positive effect on the fitness of the parasite, although that same gene can have a deleterious effect when against the genetic background of a different host. Some combinations of

host and pathogen genotypes have higher fitness than others, but the value of Θ determines whether or not these *trans*-specific gene combinations are transmitted intact across generations. Processes like genotype-specific habitat selection, co-dispersal and vertical transmission maintain high values of Θ, in the same way that inbreeding[44] or assortative mating[50] enhance the co-transmission of mitochondrial and nuclear gene combinations between parents and offspring. The presence of ecological processes that ensure the co-transmission of host and associate genes across generations affects the nature of the co-adaptive process and the degree of cooperation that is likely to evolve between species.

Just as natural selection can alter recombination rates, it can also alter co-dispersal rates (FIG. 4). Selection on genes that modify recombination rates is indirect. A modifier allele that is associated with non-recombinant haplotypes will increase in frequency, with a simultaneous decrease in recombination rate, only if non-recombinant haplotypes have higher fitness on average than recombinant haplotypes. Conversely, if these haplotypes have lower fitness on average, then recombination rates will increase. In the context of co-evolution, selection on co-transmission modifiers is similarly indirect: first, there must be variation in fitness between *trans*-specific genotype combinations; second, there must be genetic variation for co-dispersal. Only under these conditions will those alleles that modify co-dispersal, and that are associated with the fitter intergenomic epistatic combinations, increase in frequency and thereby increase the rate of co-dispersal. Theory[51–52] indicates that selection should favour any ecological process that creates and maintains an adaptive fit between genotype and context. This is the rationale behind the evolution of adaptive phenotypic plasticity[28–29]. The behaviour of newly mated queen ants that carry symbiotic mealybugs[53] (FIG. 4), or that of the bacteriocytes of aphids, which develop independently of the symbionts they shelter[54], are good examples of specific host adaptations that function to insure co-dispersal.

The theory of *trans*-specific or intergenomic epistasis allows novel and testable predictions[44]. For example, in species that undergo frequent selfing or primarily vegetative reproduction, Θ between mitochondrial and nuclear genes is high. As a result, the heritability of mitochondrial–nuclear gene combinations is also high, allowing for direct selection between favourable and unfavourable gene interactions. Such mating systems could facilitate gene transfer from the mitochondrion to the nucleus by increasing the heritability of cyto-nuclear gene combinations. Furthermore, in these mating systems, when Θ is high for mito-nuclear gene combinations, it is also high for nuclear–nuclear gene combinations. The increased heritability of these cyto-nuclear gene combinations could facilitate the adaptive changes in all components of the interaction that are necessary to achieve functional gene transfer. By contrast, mating systems in which Θ is low would militate against functional gene transfers[44].

Random genetic drift
Random changes in allele frequency from one generation to the next.

Trophophoresy
The transporting of a species that is used for food by another species.

The future of co-evolutionary genetics

The possibility of connecting the microevolutionary process of co-adaptation and the macroevolutionary pattern of co-speciation is becoming clearer. However, data are lacking on co-transmission, a key parameter that governs whether co-evolution leads to interspecific conflict with high levels of genetic diversity, or to interspecific cooperation (symbiosis) with lower levels of diversity. Very high values of Θ characterize obligate mutualisms, especially in the case of endosymbionts that have undergone substantial gene losses relative to their free-living congeners. In theory, a high level of co-transmission prohibits genomic conflict and causes mutualistic *trans*-specific co-evolution[44]. However, it is possible to argue that obligate mutualism causes high Θ rather than the reverse; to date, observations support a positive association, but do not indicate the direction of causality.

How high must co-transmission be before gene losses from an endosymbiont genome begin to occur? In genetics, a small amount of recombination can rescue a chromosome from the relentless deterioration that is caused by mutation and random genetic drift[55–56]. It might be that small amounts of horizontal transmission of endosymbionts between hosts completely mitigate the process of gene loss. It will be necessary to study mutualisms with intermediate levels of co-transmission, such as those between scolytid bark beetles and their fungi[57], or between burying beetles and their phoretic mites[58], to address this issue and to understand the limits of

Figure 4 | **Co-dispersal of host and symbiont genes.** *Acropyga* spp. ants show obligate trophophoresy with mealybugs, in which newly mated queens carry a mealybug with them when founding new colonies. At the genetic level, this is an example of the co-evolution of a mechanism for the co-transmission of host and symbiont genes. Molecular phylogenetic studies[54] have shown that this genus of ants is monophyletic, and that there are two independent origins for trophophoresy among the ants. Fossils in amber indicate that this co-evolved association is millions of years old. Other examples include: burying beetles in the genus *Nicrophorus*, which transport mites to carcasses where the mites eat the eggs of competing flies[58]; scolytid bark beetles, which transport mites that in turn transport a fungus that assists the beetles in feeding on conifers[57]; and the inherited symbiosis between grasses in the genus *Danthonia* and their epiphytic fungi[62]. Image courtesy of A. Wild, Myrmecos, Tucson, USA © (2005) A. Wild.

inference that are provided by non-genetic, economic-optimum models of co-evolution that assume that there is genomic conflict[59].

A recent comparative study of the functional transfer of mitochondrial genes to the nucleus tests the importance of co-transmission[60]. The frequency of this intergenomic transfer is highly variable across plant taxa. Co-evolutionary theory predicts that selfing or vegetatively reproducing species (with high Θ) would undergo functional transfers more frequently than outcrossing species[44]. In fact, the 19 species from outcrossing genera that have separate sexes averaged only half a transfer for each species, with no transfers at all in 12 species (63%) and few with even 2 transfers. By contrast, more than 20% of genera with the high Θ had 6 or more transfers[60]. In general, however, empirical comparative studies that use Θ are lacking. Although some evolutionary genetic models have recognized that the hierarchy of multi-species associations extends from local populations to regional communities to higher taxonomic levels[32], measures such as Θ, which estimate the degree of genetic association and that can be partitioned into hierarchical levels, are just beginning to be developed.

Many other questions remain open, including: what fraction of a genome is adapted for interactions with other species in the ecological community; how strong is selection relative to drift when acting on genes that affect interspecific interactions (that is, molecular co-evolutionary genetics); and when does microevolutionary co-evolution become a pattern of co-speciation? Nevertheless, with the growing application of molecular phylogenetics and genomics to co-evolutionary questions, the future for theoretical and empirical collaborations between ecologists and geneticists has not been so bright in several decades[61].

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