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Ehrlich and Raven escape and radiate coevolution hypothesis at different levels of organization: past and future perspectives

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The authors contributed jointly to all stages of manuscript development.

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Abstract

The classic paper by Ehrlich and Raven on coevolution will soon be 60 years old. Although they were not the first to develop the idea of coevolution, their thought-provoking paper certainly popularized this idea and inspired several generations of scientists interested in coevolution. Here we describe some of their main contributions, quantitatively measure the impact of their seminal paper on different fields of research and discuss how ideas related to their original paper might push the study of coevolution forward. To guide our discussion, we explore their original hypothesis into three research fields that are associated with distinct scales/levels of organization: 1- the genetic mechanisms underlying coevolutionary interactions; 2- the potential association between coevolutionary diversification and the organization of ecological networks; 3- the micro and macroevolutionary mechanisms and expected patterns under their hypothesis. By doing so we discuss potentially overlooked aspects and future directions for the study of coevolutionary dynamics and diversification.

Introduction

"One approach to what we would like to call coevolution is the examination of patterns of interaction between two major groups of organisms with a close and evident ecological relationship, such as plants and herbivores" (Ehrlich and Raven 1964).

In a classic paper published in *Evolution*, Ehrlich and Raven (1964) presented and discussed factors that determine food choice in phytophagous insects and how those factors would scale up to determine macroevolutionary patterns in both plants and herbivores. In this article, we celebrate Ehrlich and Raven's study, by first briefly describing their main contributions and then by describing its impact. We then explore its potential future relevance in helping the development of three different research areas, namely: the genetic mechanisms of species interactions, the assembly of species into ecological networks, and the micro and macroevolutionary consequences of coevolution. We selected these three research areas primarily because of our personal interests. In doing so, we use this opportunity to recognize and thank the long-lasting impact of Ehlich and Raven's study in our own research careers.

The Ehrlich and Raven 1964 paper

In the 1964 paper, Ehrlich and Raven started by explaining that butterfly food plant choice is: (i) restricted to geographical and ecological range, (ii) affected by oviposition and larvae choice, (iii) strongly affected by chemical factors that are repellent for most herbivores, but may be an attractant for a few, and to a less extent by mechanical defenses such as trichomes, and (iv) modified by predators and parasites, as well as ants in the case of Lycaenidae butterflies. They pointed out that "*despite all of these modifying factors, there is a general and long-recognized pattern running through the food plants of various groups of butterflies, and it is this pattern with which we shall be concerned.*"

Their inferences were based on information on the diversity of five butterfly families, and they estimated that there are 730-930 genera, of which about half had food plant records available at the time. They searched the extensive and scattered literature for food plant records and obtained information and confirmation from experts around the world. Being conservative about accepting records, they focused primarily on broad, repeatedly verified patterns of relationships. They present detailed information on the main patterns of food plant choice by each butterfly group. For example, they reported that some whites (Pierinae) feed on Capparidaceae, Cruciferae, Resedaceae, Salvadoraceae, and Tropaeolaceae, which all contain mustard oil glucosides, and that very few butterflies outside Pieridae feed on these plants. As another example, they reported that the brush-footed butterflies (Danainae) feed primarily on Apocynaceae and Asclepiadaceae, but there are also records on Moraceae and Caricaceae. All these plants have milky juice, but Apocynaceae and Asclepiadaceae also have abundant bitter glycosides and alkaloids and share at least some alkaloids and pyridines with Moraceae. They suggest that it is likely that the acquisition of the ability to feed on Apocynaceae and Asclepiadaceae opened the opportunity for the Danainae to penetrate a new adaptive zone, in which they have radiated. Their survey and evaluation point to three main implications regarding the usage of host plants by butterflies.

First, the few butterfly groups that feed on monocotyledons have ancestors that feed in dicotyledons, and that the switch from dicotyledons to monocotyledons occurred independently many times. Second, there is a general pattern that plant groups are usually fed upon by a single, phenetically coherent group of butterflies (or several very closely related groups), and that plant groups used by each group of butterflies are either very close phylogenetically or have similar chemistry. Finally, they discuss examples of plant groups, such as Araceae, that are very rarely or never utilized by butterflies, suggesting that they may have chemical or mechanical properties that render them unpalatable to butterfly larvae. They suggest that shifts into the adaptive zones represented by these plant groups have not occurred in butterflies, but they are theoretically possible and have indeed occurred by different moth lineages. They also pointed out the leading role of secondary plant substances in determining the reported patterns of host plant utilization by butterflies, and the similar effect they have for all phytophagous groups.

To explain these patterns, Ehrlich and Raven proposed a coevolutionary scenario in which occasional mutations and recombination in plants produced a series of secondary chemical compounds. Some of these compounds, by chance, reduce or eliminate the palatability of the plant that produces them, and the new chemicals may be fixed in the species by selection imposed by herbivores. With this new defense the plant escapes from herbivores and, consequently, become the ancestor of an adaptive radiation in which all the descendants share the new chemical defense. Thus, eventually what began as a chance mutation or recombination might characterize an entire family or group of related families. Later a recombination or mutation may appear in an insect population that enabled individuals to feed on some previously protected plant group. By allowing feeding on an additional food plant, this ability to overcome the plant defense would spread and become fixed in the population. This herbivore population would enter a new adaptive zone and would be free to diversify largely in the absence of competition from other herbivores. Consequently, this population becomes the ancestor of an adaptive radiation in which the descendants will feed on different species of the plant clade. In time, the process may be repeated with the evolution of new plant defenses.

Ehrlich and Raven (1964) concluded that the coevolution processes provide a starting point for understanding community evolution and suggested that similar approaches investigating stepwise reciprocal selective responses should be applied to other ecological interactions. They go as far to suggest that coevolution between interacting species groups may help solve the origin of broad patterns such as the differences in diversity between tropical and temperate areas. They conclude with a very powerful message: *"Probably our most important overall conclusion is that the importance of reciprocal selective responses between ecologically closely linked organisms has been vastly underrated in considerations of the origins of organic diversity. Indeed, the plant herbivore "interface" may be the major zone of interaction responsible for generating terrestrial organic diversity."*

The coevolutionary scenario proposed by Ehrlich and Raven was later codified by John. N. Thompson in the form of a coevolutionary hypothesis, the "escape-and-radiate" hypothesis (Thompson 1989) and a suite of predictions for the hypothesis (Thompson 2005). He emphasized that, because escape and radiate coevolution would produce starbursts of speciation in interacting lineages, cospeciation – i.e., matching phylogenies at the species level – could not result from the hypothesized process. That is, adaptation and speciation are partially decoupled in escape-and-radiate coevolution.

Different coevolution concepts before and after Ehrlich and Raven 1964

Ehrlich and Raven were not the first to develop the idea of coevolution. The main idea of Ehrlich and Raven's coevolutionary scenario, that plant-herbivore interactions affect diversification of both groups, have been previously studied (e.g., see reviews by Thompson 2005 and Janz 2011). Darwin discussed how plants and insect pollinators could evolve through reciprocal evolutionary changes, even though he did not use the term coevolution (Darwin 1859). Müller (1879) created a mathematical model - probably the first application of mathematics on evolution studies - to explain how interactions may shape traits in mimetic butterflies. Flor (1955) developed the concept of gene-for-gene interaction to explain variation in resistance and virulence in a plant-pathogen system. Mode (1958) used the proposed gene-for-gene mechanism to develop the since then influential mathematical model of coevolution. Pimentel (1961) developed the idea that reciprocal genetic changes can regulate population size in resource-consumer interactions. Even though the idea of coevolution was already there, it was Ehrlich and Raven's thought-provoking publication in 1964 that popularized the term coevolution, impacting ideas even outside biology (O'Reilly et al. 2020). During those same years, Janzen's (1966) landmark studies on coevolution of plants and ants, and Smith's (1970) studies of coevolution of pines and squirrels, were published and influenced subsequent studies especially in evolutionary ecology.

Ehrlich and Raven's scenario was intended to explain diversity of plants and herbivores by the process of increased cladogenesis in enemy-free space for plants and competitor-free space for herbivores. Many recent reviews addressed the ideas of coevolution and coevolutionary diversification in insect-plant interactions (Rausher 2001; Thompson 2005; Agrawal 2007; Janz 2011; Althoff et al. 2014; Suchan and Alvarez 2015; Agrawal and Zhang 2021). During the 1960s and 1970s the word coevolution was used in an overly broad sense, meaning the adaptation of one species to the traits of the species with which it interacts. Coevolution became "*synonymous of anything having to do with interactions between species*" (Thompson 1994). Some authors advocated for the restricted use of the term for just the reciprocal selection imposed by the ecological interaction between two or more species (Janzen 1980; Thompson 1982; Futuyma and Slatkin 1983). In subsequent years, researchers characterized a range of coevolutionary patterns and processes at both the microevolutionary and macroevolutionary scales (Thompson 1989). Some of the different related coevolution concepts can be classified as follows: (1) *pairwise (specific) coevolution* – the adaptive response of two species to evolutionary changes in each other and examples of pairwise coevolution include *gene to gene* correspondence between the traits evolving in the two species and the *coevolutionary arms race* in which there is an escalation of traits in one species and the counter responses in the other; (2) *diffuse (guild) coevolution* – reciprocal adaptation of a group of ecological similar species to selection imposed by another group of species. Both pairwise and guild coevolution can foster *diversifying coevolution* (Thompson 2005). *Diversifying coevolution* includes distinct coevolutionary dynamics that promote diversification of interacting species. *Escape-and-radiate coevolution* is one particular form of diversifying coevolution in which guilds of interacting species affect the diversification across broad temporal and spatial scales. All these concepts relate to the idea of reciprocity, meaning the interacting species affect each other's evolution (Thompson 1989; Janz 2011), but represent different processes occurring at different scales. Hypotheses on how adaptation and speciation occur during the coevolutionary process have continued to be refined and expanded in recent decades (Thompson 2013).

Ehrlich and Raven coevolution's model does not specify how the fixation of a character that increases individual fitness (a chemical defense or the herbivore ability to overcome a plant defense) would lead to a higher diversification rate. Independently of the mechanism connecting fitness to diversification, a common misunderstanding about Ehrlich and Raven coevolution's model is that their coevolutionary scenario involving plants and herbivores would require a simultaneous *co-diversification* - coincident diversification between two interacting species - and lead to *parallel cladogenesis* – the phylogenetic relationships of plants is mirrored by phylogenetic relationships of an interacting herbivores (Thompson 2005). In contrast, escape-and-radiate dynamics predict bursts of asynchronous diversification which, in turn, implies that co-diversification and parallel cladogenesis are not only unlikely to occur but actually evidence against the escape-and-radiate dynamics (Thompson 2005). Indeed, the adaptive radiation of the herbivorous insects largely postdates the radiation of the plants (Mitter and Brooks 1983; Futuyma and Keese 1992). This much earlier diversification of plants implies that the selection for the evolution of a particular chemical defense was imposed by herbivores other than the ones currently associated with the plant species, as clearly recognized by Ehrlich and Raven (1964).

Bibliometric analysis

We explored the impact of Ehrlich and Raven (1964)'s paper (hereafter E&R paper) in the literature by searching the ISI Web of Science for the papers that cited it. Our search, performed on May 4th, 2021, found 2,489 scientific papers citing E&R paper. We then explored how those papers were distributed across scientific fields of study by extracting the authors' keywords and additional keywords assigned to the paper, i.e., "keyword plus". We recorded 9,095 keywords and investigated their co-occurrences using a network framework (Figure 1). We used a two-step process to analyze the co-occurrences among keywords. First, we cleaned our dataset of typos and truncated keywords. Then, we synonymized words with different spellings (e.g., defense and defence) or that were too similar in meaning (e.g., insect herbivore and herbivorous insect). Although the latter criteria is subjective, it heuristically allowed us to circumvent the problem of ignoring the impact of E&R paper in a given field because multiple similar keywords were used. The vast majority of keywords were singletons (n = 6236 keywords, 68.56%) and 98.68% of the keywords were present in less than 30 papers. In contrast, just 22 keywords were presented in more than 100 documents (Table S1).

We then explored patterns of co-occurrence of keywords as a bibliometric network in which nodes describe keywords and there is a link connecting two keywords if these are present in the same paper. We focused our analysis on the more common keywords that were recorded in at least 15 papers (n = 271 keywords) but we removed the two most used keywords "evolution" and "coevolution" because their wide presence in our dataset in the documents would blur the emergence of modules of co-occurred keywords, i.e., groups of keywords that occurred more frequently in the same document than with other keywords. We identified modules by using a smart local moving algorithm (Waltman and van Eck 2013) that optimizes a modularity function (Waltman et al. 2010). All analyses were performed in VOSviewer 1.6.16 (van Eck and Waltman 2010). We used the default parameters of VOSviewer to identify modules in the network (attraction = 2.0, repulsion = 0.0, resolution = 1.0) performing full counting of co-occurrences between keywords, association strength normalization (Waltman et al. 2010), and allowing the algorithm to merge small modules.

Our analysis indicates four different modules, mapping to different areas of evolutionary and ecological studies (Figure 1). Two modules were directly associated with plant-herbivore interactions. The first module is formed by studies on chemical ecology of plant-herbivore interactions (red module, Figure 1). Among the main keywords associated with this module include “resistance”, “herbivory”, “tolerance”, and “chemical defense”. The second module focuses on studies of biology of herbivorous insects, in particular butterflies (yellow module, Figure 1), and it is characterized by the following keywords “Lepidoptera”, “performance”, “preference”, and “oviposition”.

The next two modules are associated with broader implications of E&R’s ideas to evolution (blue module, Figure 1) and ecology (green module, Figure 1). The blue module is formed by genetic, phylogenetic and macroevolutionary studies, as indicated by keywords such as “diversification”, “molecular phylogenies”, “speciation”, “adaptive radiation”, and “mitochondrial DNA”, despite the fact "macroevolution" itself is on the green module. Among evolutionary studies, our citation analysis suggests that E&R paper did not equally permeate the paleontological and evolutionary ecology literature. There are very few keywords that are typical paleontological keywords (e.g., “fossil record”, at the blue module, which only shows up 16 times). It is interesting to note that the macroevolution papers that typically cited E&R paper were those that used phylogenies (mostly molecular) to study macroevolutionary patterns (Figure 1).

Finally, the green module, in contrast, is characterized by studies of ecological patterns and processes, especially on (plant) community ecology (Figure 1). Among the keywords characterizing the green module are: “plant”, “diversity”, “patterns”, “ecology”, “community”, and “species richness”. Having said that, the green module also shows keywords associated with evolutionary processes at different scales, such as “local adaptation”, “geographic mosaic of coevolution”, “arms race”, and “macroevolution”. It is also interesting to note that many ecological interactions are spread across different modules, as illustrated by “herbivory” (red module), “parasitism” (yellow module), “mimicry” and “mutualism” (blue module), and "competition", "predation", and "ecological network" (green module). Thus, different types of ecological interactions are associated with different combinations of keywords, which may indicate that different studied systems have been used to explore different consequences of ecological interactions - and the ideas of Ehrlich and Raven - in evolution and ecology.

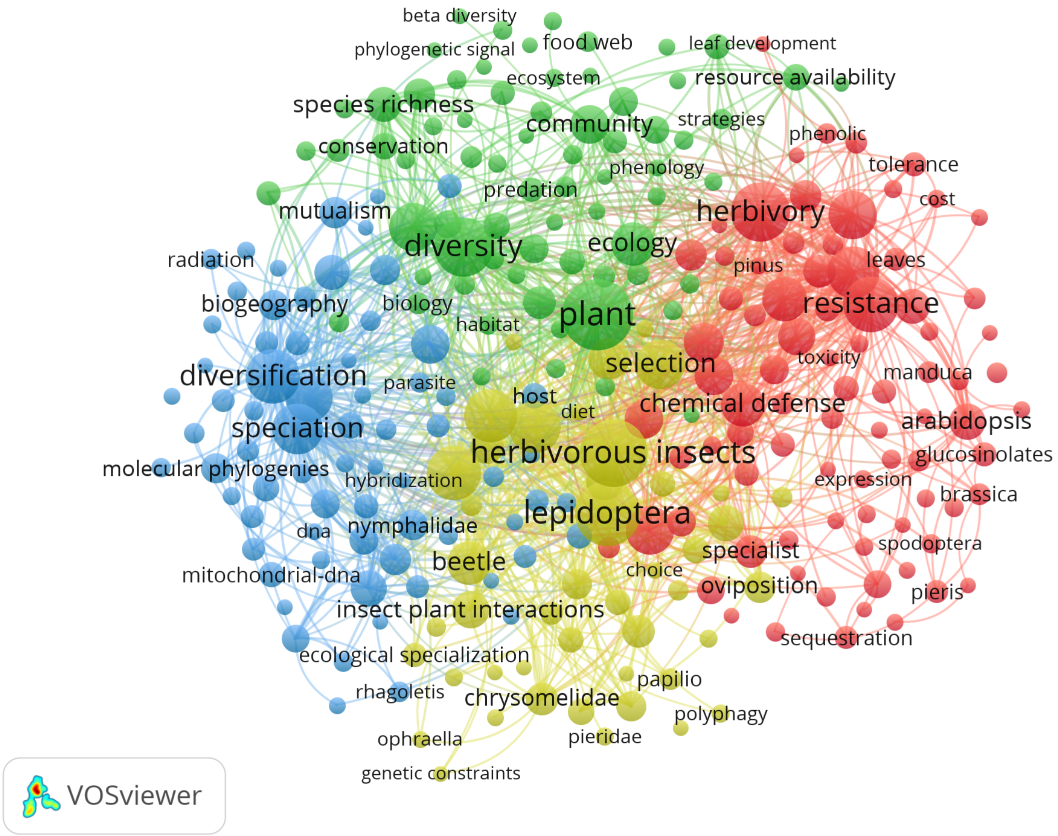

Figure 1. Bibliographic network of papers that cite Ehrlich and Raven 1964's describing words as nodes and in which two words were connected if they were present as keywords in the same document. Node size is proportional to the sum of association strengths of the word in the network. The pairwise association strength is a measure of similarity between the set of documents in which two words were presented as keywords (Waltman et al. 2010). Colors identify four modules that we associate to four major fields in which Ehrlich and Raven 1964's paper have an impact: (green) community ecology, (red) chemical defence of plant-herbivore interactions, (yellow) insect (mostly butterfly) - plant interactions, and (blue) mostly phylogenetic and macroevolution. The keywords "evolution" and "coevolution" were removed

prior to the analysis because they were too common (see Table S1) and were obscuring the underlying pattern.

The origin of adaptations in plants and herbivorous insects: chance mutations and recombination

The E&R paper was published about a decade after Watson and Crick discovered the DNA double helix structure and two decades before PCR was invented. At that time there was very limited knowledge on the molecular mechanisms behind organisms' adaptations. A key aspect of the coevolutionary escape and radiate hypothesis they proposed were the origin of adaptations in plants and herbivores. They said *"Angiosperms have, through occasional mutations and recombination, produced a series of chemical compounds not directly related to their basic metabolic pathways but not inimical to normal growth and development. Some of these compounds, by chance, serve to reduce or destroy the palatability of the plant in which they are produced"* and that *"if a recombinant or mutation appeared in a population of insects that enabled individuals to feed on some previously protected plant group, selection could carry the line into a new adaptive zone"*. In the past few decades, with the technological revolution in molecular biology and genomics, there have been many discoveries of the detailed molecular mechanisms behind these adaptations, and in many cases complex adaptations such as the ability to feed in a toxic plant can evolve with just a few mutations (e.g., Zhen et al. 2012).

Recent decades have also produced great advances in the molecular mechanisms and evolutionary origins behind important secondary metabolites. For example, pyrrolizidine alkaloids, a typical plant secondary metabolite that acts as a defense against herbivores. Homospermidine synthase, a specific enzyme for pyrrolizidine alkaloids synthesis, evolved by duplication of a gene involved in primary metabolism. This gene duplication occurred several times independently in different angiosperm lineages (Ober and Kaltenegger 2009). Another example is the evolution of the pathway to produce nicotine, a defensive neurotoxin against herbivores, in wild tobacco. Xu et al. (2017) showed that nicotine biosynthesis evolved by the duplication of two ancient primary metabolic pathways. They also showed that transposable elements (TEs) derived transcription factor binding motifs may be responsible for coexpression of the genes in the pathway. This study shows the importance of the interplay of gene duplications and transposable element insertions in the evolution of specialized secondary metabolite pathways.

Accordingly, we have now many examples on the molecular variation that gave rise to herbivore adaptations to overcome plant chemical defenses. Examples include the flavin-dependent monooxygenase system in arctiid moths used against pyrrolizidine alkaloids (Naumann et al. 2002), the cytochrome P450 monooxygenase gene family in *Papilio* butterflies used against furanocoumarins (Li et al. 2003), modifications in the alpha subunit of the sodium/potassium-transporting ATPase (ATPα) that allow insects to feed on plants containing cardenolides (Zhen et al. 2012), a glucoside malonyltransferase enzyme used to detoxify phenolic glucosides in whiteflies (Aleyrodidae) (Xia et al. 2021), and glucosinolate sulfatase in a plutellid moth (Ratzka et al. 2002), and nitrile-specifying protein in pierid butterflies (Wittstock et al. 2004), both used against toxic glucosinolates.

Three examples deserve further discussion. First, in the case of the identification of the nitrile-specifying protein gene in pierid butterflies that detoxify glucosinolates, this key innovation was linked to macroevolutionary patterns (Wheat et al. 2007). By studying many species of the Pieridae butterfly family, Wheat et al. (2007) showed that the nitrile-specifying protein activity matched the presence of glucosinolate in the host plant. They also constructed calibrated phylogenies and concluded that this enzyme evolved shortly after the diversification of the host plant Brassicales. They also showed higher diversification rates in pierid clades that colonized the Brassicales (Wheat et al. 2007). These observations are predicted by the escape-and-radiate hypothesis.

Second, many insects, such as the monarch butterfly, can feed on cardenolides containing plants and even sequester some cardenolides to become resistant to predators. By comparing sodium/potassium-transporting ATPase (ATPα) sequences of 14 species that feed in cardenolide containing host plants, Zhen et al. (2012) showed that amino acid substitutions in cardenolide feeding species are highly clustered with many parallel substitutions, a strong evidence for convergent evolution. Later, Karageorgi et al. (2019) expanded this work to combine convergent evolution with CRISPR–Cas9 genome editing technology to validate the patterns of molecular variation in whole organisms. They observed convergent mutations in insects from six orders that independently colonized cardenolid-containing plants. When they edited the native ATPα gene in *Drosophila melanogaster* and introduced the three most common mutations present in cardenolid feeding insects, they produced flies that were as resistant to cardenolides as monarch butterflies and were able to retain small amounts of cardenolides through metamorphosis. It is amazing that only three mutations can make fruit-flies as resistant to cardenolides as monarch butterflies. This example illustrates how different herbivore clades could in principle colonize novel hosts, as predicted in the E&R paper.

Third, it was recently discovered that the ability of whiteflies to neutralize host-plant phenolic glucosides occurred by an exceptional horizontal gene transfer event of a plant-derived phenolic glucoside malonyltransferase gene (Xia et al. 2021). While the importance of horizontal gene transfer has been widely recognized in prokaryotes, only recently studies have shown its importance in eukaryotes' adaptations. In arthropods, horizontal gene transfers seem common from microorganism donors, so this plant-to-insect horizontal gene transfer event seems very unique (Xia el al. 2021). It is an interesting case in which an herbivore has adopted their opponent's combat strategy to resist it, providing a novel mechanism that could speed up a macroevolutionary arms race between plants and herbivores.

The genes associated with traits that are important for ecological interactions have also been identified in other types of interactions such as predation (Barrett et al. 2019), host- parasite (Cogni et al. 2016), and pollination (Fattorini and Glover 2020). But still, we have no knowledge on the molecular variation responsible for the vast majority of key plant defenses and herbivore counteradaptation traits, as well as key traits in other types of ecological interactions. Additionally, in just a very few plant-herbivore systems we know the mechanism of both the plant defense and the herbivore counteradaptation. We expect great advances in this area due to development of increasingly sophisticated and affordable molecular and genomic methods.

The discovery of genes associated with key traits is essential for a golden standard in current evolutionary biology, namely linking genotypic variation, phenotypic variation, and fitness in wild populations (Feder and Mitchell-Olds 2003; Hoekstra 2010). We believe future studies should try to link genotypic, phenotypic and fitness variation in traits important for ecological interactions. For example, Carley et al. (2021) investigated ecological and genetic processes acting on a molecular polymorphism associated with variation in leaf chemical profiles in the wildflower *Boechera stricta* (Brassicaceae). They showed balancing selection on the alleles associated with leaf chemical profiles by contrasting fitness effects across environments caused by herbivory and drought. Studies like this are crucial to understand how natural selection acts on key traits to ecological interactions.

However, a great challenge in the escape-and-radiate coevolution model is to understand how the fixation of a key trait in a population can affect cladogenesis (see discussion below). Here, knowing the genes associated with key traits for ecological interactions can also help. We can use experimental approaches to test how herbivory may lead to local population extinction and affect extinction probability of incipient species. A promising approach for future studies is to experimentally test how plant defenses may affect herbivory and consequently plant populations and patterns of interaction between plants and herbivores at the local level. If the molecular details of a particular plant defense are known, it is possible to produce transgenic plants lacking the defense and the effect of herbivores on those plants can be tested under field conditions (e.g., Steppuhn et al. 2004).

The escape-and-radiate hypothesis and its potential consequences for ecological networks

Our analysis of keyword co-occurrences indicates that community ecology is one of the fields impacted by E&R's study (green module, Figure 1). This is not surprising. The very first sentence of their study focuses on "*community evolution*", specifically, on "*evolutionary interactions found among different kinds of organisms*". The first paragraph of their manuscript also emphasizes the overlooked role of "*reciprocal aspects of these interactions*" on "*the understanding of organic diversification*"(Ehrlich and Raven 1964). In the past decades, we progressed in our understanding of the organization and the underlying evolutionary processes shaping interacting assemblages. In this sense, interacting assemblages often show nonrandom patterns of interaction that can be quantified through network descriptors (Pascual and Dunne 2006). Hence, network descriptors may provide fingerprints of evolutionary and ecological processes that shape and are shaped by ecological interactions (Pascual and Dunne 2006; Bascompte and Jordano 2013).

Network ecology has provided insights into the trophic organization (Elton 2001; Cohen and Stephens 2020) and stability (May 1973) of ecological communities, and the flow of information (Margalef 1996), energy and matter (Odum 1960; Hannon 1973) in ecosystems. Network thinking underlies the understanding of the empirical results that revealed how indirect effects can shape diversity patterns (Paine 1966; Estes et al. 2013) and in studies showing how coextinction may imperil interacting assemblages (Memmott et al. 2004; Rogers et al. 2017). Similarly, network thinking has been used to explore a number of evolutionary problems, including (i) the emergence of evolutionary innovations (Wagner 2011); (ii) the way ecological interactions are associated with particular coevolutionary dynamics (Fonseca and Ganade 1996), reshape adaptive landscapes (Kauffman and Johnsen 1991), and fuel the evolution of novel lifestyles (Thompson 2005); and (iii) how evolution and coevolution may favor species-rich networks to emerge (Loeuille and Loreau 2005; Montoya 2007; Peralta 2016; Harmon et al. 2019; Ponisio et al. 2019).

In contrast to its foundational role in the study of community evolution, the exploration of E&R hypothesis is very limited in the study of ecological networks (Braga et al. 2018; Harmon et al. 2019). E&R hypothesis is often used to illustrate the potential of interactions to fuel biodiversity, but testing the conditions in which escape-and-radiate coevolution would shape or be shaped by ecological networks are rare (Braga et al. 2018; Harmon et al. 2019). This absence of tests might be partially a consequence of the ER hypothesis being inherently difficult to test. Moreover, multiple ecological and evolutionary processes may generate network patterns at the community level, masquerading the potential causes of observed patterns (Guimarães 2020).

In trying to understand how escape-and-radiate dynamics may affect the network structure, a fundamental problem is to define the relevant temporal and spatial scales. Thus, although aiming in understanding community coevolution, escape-and-radiate hypothesis is a macroevolutionary hypothesis (Hembry and Weber 2020) on exploring how *"patterns of interaction between two major groups of organisms with a close and evident ecological relationship"* (Ehrlich and Raven 1964) is associated with the diversification of these groups across large spatial and longer temporal scales. Thus, clade-based networks depicting interactions among species (or higher taxa) of two (or more) clades across large spatio-temporal scales might be a more natural system descriptor than the local ecological, species-based networks often studied in community ecology (Guimarães 2020).

Once the relevant temporal and spatial scales are defined, the most fundamental attribute of an ecological network is its species richness. From an evolutionary point of view, the crux of the problem is the link between adaptation of traits of interacting species in a network with diversification of clades. Escape-and-radiate dynamics predicts an increase in the diversity of interacting assemblages. This increased diversity generated by diversification promoted by coevolution actually makes the escape-and-radiate hypothesis distinct from most putative coevolutionary processes. Indeed, just a small fraction of potential coevolutionary dynamics would favor speciation and diversification (Thompson 1989; Hall et al. 2020), i.e., diversification can be generated by coevolution but coevolution does not imply diversification (Page 2003; Thompson 2005). Rather, coevolutionary models of small networks of interacting hosts and parasites indicate the possibility of trait change without generating arms races (Nuismer and Thompson 2006).

In systems in which coevolution favors diversification, i.e., diversifying coevolution, escape-and-radiate is only one possible way to foster species-rich networks. Indeed, the geographic mosaic of coevolution may favor speciation

(Thompson 2009), but this diversification mediated by coevolution may not show sequential bursts of diversification expected by escape-and-radiate dynamics. Alternatively, ecological interactions may fuel diversification without necessarily involving coevolution (see review by Hembry and Weber 2020). Finally, coevolution may allow ecological networks to collect species, leading to increased diversity of local ecological networks (Thompson 2005; Bascompte and Jordano 2013), without necessarily affecting speciation and diversification rates. Indeed, increased diversity of ecological networks may be a result of ecological sorting, without direct impact of the coevolutionary process. Thus, although escape-and-radiate dynamics favors species-rich networks, multiple processes, including - but not limited to - other forms of coevolution, may also generate the same pattern.

Escape-and-radiate dynamics may favor particular patterns of interaction in ecological networks. As described by Harmon et al. (2019), the initial condition of these networks would be specialized herbivores feeding in one or a small group of plant species (Figure 2a). The evolution of a defense against herbivores would disconnect the plant species from the network (Figure 2b). The plant species diversify in the new adaptive zone (Figure 2c). Then, the evolution of counter-defenses in an herbivore allows it to colonize the plant species (Figure 2d,2g) and then diversify (Figure 2e-f, 2h-i). However, small differences in the macroevolutionary arms race may lead to large differences in network structure. For example, if the colonization of new hosts imply the loss of the interactions with previous hosts (host shift or interaction rewiring; figure 2d), this macroevolutionary arms race operating iteratively would build up an ecological network characterized by modules of interacting species (Figure 2d-f). Indeed, some forms of plant-herbivore interactions often show highly modular networks at different levels of organization (Meskens et al. 2011; Pires and Guimarães 2013; Lau et al. 2016; Braga et al. 2018; Cosmo et al. 2021) and modules may be the outcome of diversification process (Qin et al. 2018).

Modularity, however, is a possible but not unavoidable outcome of escape-and-radiate dynamics. If interactions with ancestral hosts are kept after novel host colonization, the resulting network would be much different: older herbivore species interact with a subset of the hosts of the younger species, leading to a nested pattern (Figure 2g-i). Although insect herbivores are often specialists (Fontaine et al. 2009), there is also evidence that lineages of herbivore insects retain the ability of using the ancestral hosts. By retaining the ability of using ancestral hosts, alternative macroevolutionary dynamics may be generated, in which specialization in lineages oscillates across time (the oscillation hypothesis, Nylin and Janz 2008; Nylin et al. 2018), leading to nested host ranges across clades of herbivores (Braga et al. 2018). Thus, extreme variation in network structure will depend on details of the escape-and-radiate dynamics, such as the likelihood of a novel herbivore species to retain the interactions of their ancestral species in addition to exploring the formerly unavailable plant resources (Braga et al. 2021). In this sense, the complex network patterns empirically observed in plant-butterfly networks suggest that the interplay between host switching and host retention is shaping diversification and patterns of interaction between plants and herbivores across large temporal scales (Braga et al. 2018, 2021).

Hence, when host switching prevails, escape-and-radiate dynamics foster the emergence of modular networks. It is important to note that other processes may also lead to modular ecological networks. For example, modules may be generated by different macroevolutionary regimes (Braga et al. 2018, 2021) or by arms race dynamics without diversification (Andreazzi et al. 2017). Moreover, ecological dynamics in antagonisms may favor the emergence of modules due to habitat heterogeneity (Pimm and Lawton 1980) or to differential extinction of interacting species (Thébault and Fontaine 2010). Therefore, as in the case of species richness, particular network structures can be generated by escape-and-radiate dynamics, but these patterns may have other alternative explanations. In this context, a route to detangle the processes that are indeed shaping ecological patterns is to explore associations between these patterns and the evolutionary history of the organisms.

For example, escape-and-radiate dynamics is often used to justify phylogenetic patterns in local interacting networks (Joppa et al. 2009; Tallamy and Shropshire 2009; Burghardt et al. 2010; Jorge et al. 2017; Wang et al. 2020). Having said that, escape-and-radiate dynamics predicts a very specific scale in which network patterns should be associated with phylogenies: at the module level. A strong phylogenetic signal at the module level is expected because, if complete host shifting is occurring, each module will be mostly formed by closely-related species of both plants and herbivores. In contrast, at the level of the entire network (i.e., including all species of both interacting clades), escape-and-radiate dynamics does predict weak phylogenetic patterns (e.g., no co-phylogenies) because diversity increases as a consequence of the burst of diversification resulting from the colonization of novel adaptive zones by hosts and herbivores (Thompson 2005). These bursts are expected to show no pattern of co-diversification because they occur asynchronously and because the herbivores colonizing a novel plant host are not necessarily from the lineage that explored the ancestrals of the novel host (Thompson 2005). Accordingly, at the within-module level, multiple ecological processes, such as neutral, abundance-based effects on interaction patterns and geographic mismatch among different partners, may blur phylogenetic patterns of interaction (Lewinsohn et al. 2006), leading to weak phylogenetic patterns. Phylogenetic-based modules are indeed observed in intimate plant-herbivore interactions showing extreme levels of modularity (Prado and Lewinsohn 2004; Thébault and Fontaine 2010; Pires and Guimarães 2013). Interestingly, the same is true for some intimate mutualisms, such as the interactions between ants and myrmecophytes (Fonseca and Ganade 1996). If the same macroevolutionary processes are shaping the tight association between phylogenies and modules in disparate mutualisms and antagonisms is still an open question.

To sum up, E&R’s hypothesis has had a major impact in community ecology and, as originally formulated, is strongly associated with the role of patterns of interaction in species-rich assemblages on macroevolution. These patterns of interaction can be described through networks, but E&R’s hypothesis generates patterns similar to those predicted by a myriad of ecological and evolutionary models. Escape-and-radiate dynamics combines multiple elements in a single model, such as coevolutionary arms races, adaptive zones, specialization, geographic spreading, speciation, and interaction rewiring. Small changes in the fundamental aspects of the escape-and-radiate dynamics may lead to disparate network structures (Figure 2). We can improve our understanding of how coevolution shapes networks at long temporal scales by exploring the role of each of these components independently. By doing so, we would be able to create and test a theoretical map on how distinct elements of coevolutionary dynamics shape particular network patterns. Moreover, by building up this theoretical map, we could also explore which network patterns are more likely to favor diversification (Bakkes et al. 2021).

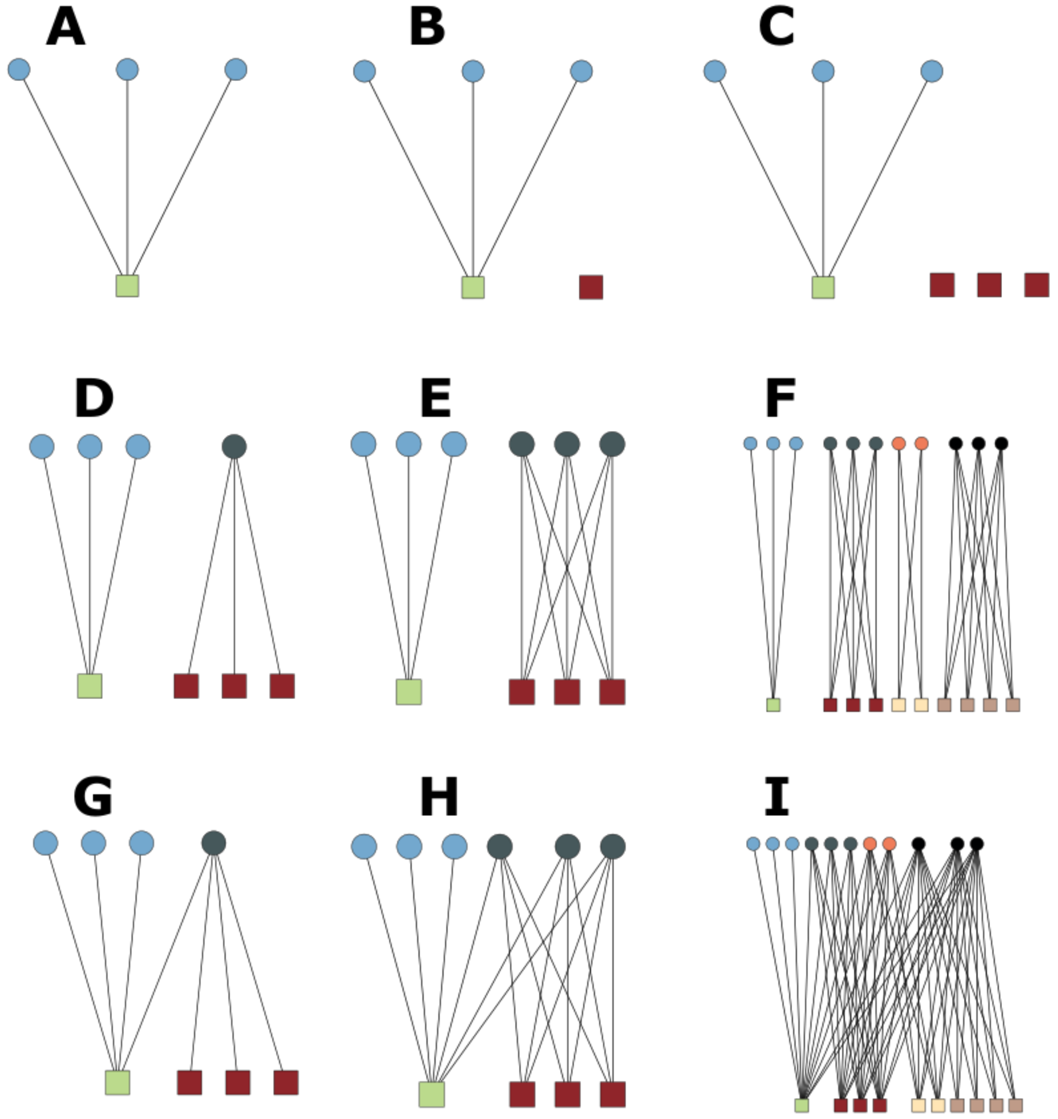

Figure 2. Escape-and-radiate hypothesis may generate distinct network structures depending on the details of the coevolutionary process, based on Braga et al. 2018 and Harmon et al. 2019. (A-I) Plant species are depicted as squares and herbivore species as circles. Colors indicate the same defenses (in plants) or the counter-defenses (in herbivores). (A) A plant species hosts herbivore species, (B) The evolution of a new defense allows the emergence of a new species in an enemy-free adaptive zone. (C) The new plant species diversify. (D) The evolution of a counter-defense allows host switching and the formation of a new herbivore species. (E) Herbivore species diversify, (F) the repetition of steps C and D lead to the formation of a highly modular

network. (G-I) the same sequence as in D-F but now colonization of a novel host does not imply a host switch, leading to a nested network.

Predictions, limitations and empirical work of the escape-and-radiate hypothesis at the macroevolutionary scale

Ehrlich and Raven (1964) argued that species interaction can act as a relevant motor of diversification, but the lack of phylogenies, a adequate fossil record, and suitable comparative methods precluded direct macroevolutionary tests of the escape-and-radiate hypothesis for several decades (Futuyma and Agrawal 2009). In their own words: "*Although the data we gathered permit us to make some reasonable sequence predictions about phylogenetic patterns (e.g. diversification of Apocynaceae and Solanaceae before Danainae and Ithomiinae, respectively), these predictions cannot be tested and the relationships cannot be specified further in the absence of a fossil record. The reconstruction of phylogenies on the basis of this sort of information would seem an unwarranted imposition on the data, since evolutionary rate and time are still inseparable*". Since the original publication by Ehrlich and Raven (1964) the field of macroevolutionary has seen a spectacular accumulation of molecular phylogenies, new dating approaches that combine DNA sequences with the fossil record, and the development of new comparative tools. Curiously, there are still a small number of empirical studies on the macroevolution of insect-plant interactions using molecular phylogenies and the comparative methods (Suchan and Alvarez 2015; Jousselin and Elias 2019). Moreover, revaluations of macroevolutionary predictions of the escape-and-radiate hypothesis using the comparative methods and phylogenies have casted doubt on some previous results, for example on how plant defenses might or not increase diversification rates (e.g., Foisy et al. 2019).

Although the paleontological community (another field interested in the controls of diversification) has also shown some interest in the role of species interactions on diversification, the prevalent perception was for quite a while, that abiotic factors, not biotic interactions, might be a more relevant motor of diversification at deep time and large spatial scales (Benton 2009). Even though some early paleobiology work, with clear overlap with the escape-and radiate hypothesis, strongly advocated for the role of species interactions in deep time diversification (Van Valen 1973; Vermeij 1977, 1994; Sepkoski 1996), and the role of species interactions has gained recent support in paleobiology (e.g., Ezard et al. 2011; Liow et al. 2015; Silvestro et al. 2015), most recent studies have focused on just one form of species interaction: the interspecific competition. Hence, we feel that the effect of species interaction on diversification still needs further empirical scrutiny, and the escape-and-radiate hypothesis might serve as a fruitful venue to do that, in particular if the crosstalk between neontologists and paleontologists is further promoted.

Our literature analysis suggests that even though the Ehrlich and Raven (1964) paper had a very strong impact in community, chemical and insect ecology (figure 1), we suspect that not enough crosstalk on how antagonistic interactions, such plant-herbivore interactions, might affect diversification dynamics have happened between neontologists and paleobiologists. This is evidenced in our bibliography analysis in the "diversification" module which shows keywords that are usually related to the neontological research using molecular phylogenies to study the macroevolutionary aspects of the escape-and-radiate hypothesis (e.g., "molecular phylogenies", "dna", "mitochondrial dna", "speciation"), and just a few words that are typical of the paleontological literature (e.g., "fossil record"). Other words related to paleontological literature, such as "macroevolution" and "extinction" are used in strong association of ecological keywords, suggesting they are used in the context of ecological studies (green module). Of course, paleobiologists are aware of Ehrlich and Raven's work (e.g., Vermeij 1994; Jablonski 2008), and the views of neontologists are influenced by paleo literature (e.g., Hembry and Weber 2020), but given how the subsequent discussions on the underlying mechanisms of the escape-and-radiate hypothesis unfolded (e.g., Althoff et al. 2014; Maron et al. 2019), we suspect that this lack of crosstalk might have hindered a broader discussion on ideas related to the escape-and-radiate hypothesis. In particular, we argue that this lack of exchange might have predisposed evolutionary ecologists to overlook potential relevant mechanistic routes underlying the escape and radiate hypothesis, most notably the potential effect of coevolution on extinction dynamics at population and macroevolutionary scales.

The escape-and-radiate coevolution and its overlooked potential consequences for extinction dynamics

Futuyma and Agrawal (2009), Janz (2011), and Nylin and Wahlberg 2008, (and likely few others) briefly mention (in one sentence each, typically with no further discussion on mechanisms) that an adaptive trait allowing insects to overcome plant defense could in theory lower insect extinction probability, but most evolutionary studies that followed the E&R paper typically focused on mechanisms leading to changes in speciation rate. Those mechanisms have been discussed in terms of how coevolution might directly or indirectly increase speciation rate (e.g., Althoff et al. 2014; Maron et al. 2019). Although it is quite possible that most mechanisms act through speciation dynamics, it is striking to see the paucity of discussion on mechanisms acting through extinction. This is relevant given that in theory an increase in diversification rate (a prediction of the escape-and-radiate hypothesis) could be produced either by an increase in speciation as by a decrease in extinction rate.

It is worth emphasizing that several empirical examples (e.g., Farrell et al 1991; Farrell 1998; Wheat et al. 2007; Winkler et al. 2009) of the escape and radiate hypothesis have detected an increase in net diversification (speciation minus extinction) not in speciation *per se*. Although there are few examples suggesting that the interaction might indeed affect speciation rate *per se*, one should note that: 1- those are not abundant (see review by Jousselin and Elias 2019); 2- the few studies showing such effect typically do not control for confounding effects (Jousselin and Elias 2019); 3- estimating extinction from molecular phylogenies (the prevalent approach to study coevolutionary diversification) is very difficult (Rabosky 2010); 4- simulation studies have shown that model inference using molecular phylogenies might wrongly suggest changes in speciation rate when in reality change in extinction rate were simulated (Burin et al. 2019); 5- recent theoretical work has casted serious doubts on our ability to properly differentiate different diversification models solely using molecular phylogenies (Louca and Pennell 2020); 6- empirical studies are concentrated in few phylogenetic groups (Jousselin and Elias 2019).

Hence although it is intuitive to think, and in fact likely, that coevolution might result in an increasing speciation rate, we still lack ample and solid direct evidence of that at the macroevolutionary scale (see review by Jousselin and Elias 2019). Moreover, it might be interesting to explicitly consider the potential effects of coevolution on extinction rates, which at first might be seen as a "non-intuitive" mechanism. We suspect it might be more relevant than previously thought, as indicated by studies suggesting coevolution may be a fundamental process shaping population persistence at short temporal scales (Thompson 2005)

This proposal is also motivated by paleontological results that suggest "non-intuitive" controls of biodiversity and those that suggest that extinction is indeed a relevant macroevolutionary process. For example, Bambach et al. (2004) made the intriguing suggestion that 2 out of the 5 so-called “mass extinction events”, might have been more controlled by a drop in origination than a rise in extinction *per se*, suggesting renaming those events “mass-depletions”. Additionally, diversity declines, so commonly seen for several clades in the fossil record, might be equally controlled by a lack of speciation as by a rise in extinction rate *per se* (Gilinsky and Bambach 1987; Quental and Marshall 2013). Although those two examples underplay the role of extinction dynamics, they illustrate what we call “non-intuitive'' controls of biodiversity, which might characterize the effect of coevolution on extinction dynamics rather than speciation. Lastly, and perhaps more akin to our general argument on the potential effect of coevolution on extinction, some radiations such as the rise in family diversity of Holometabolous insects might be more affected by a drop in extinction than a rise in origination *per se* (Nicholson et al. 2014).

As discussed for speciation (Janz 2011; Althoff et al. 2014), it will be important to think of the potential direct and indirect effects of coevolution on extinction. The possibility that coevolution between herbivores and plants results in direct effects on extinction involve ideas such as the acquisition of plant defenses lowering the probability of extinction. The plausibility of such direct mechanisms rests on the idea that herbivory should have a direct effect on individual plant survival and reproduction, and that such effects would cascade up to affect population demography and eventually the species persistence. Herbivory has been shown to reduce plant reproduction or growth (Crawley 1989; Ancheta and Heard 2011), and even lead to individual plant death (Crawley 1989). Although Crawley (1989), at the time of his review, did not argue that such effects would necessarily translate into a significant population suppression, there is now growing evidence that herbivory might indeed affect plant population demography (Ancheta and Heard 2011; Myers and Sarfraz 2017) and even drive local populations to extinction (e.g., Schöps 2002), at least for rare plants species or for those with fragmented populations. It is unlikely that all herbivores will impose such detrimental effects, and very likely that the effect on host plants is context dependent (Myers and Sarfraz 2017), but there is at least evidence that herbivores might affect individual plant fitness, survival and population demography. Hence it is at least possible that escaping herbivory might indeed lower extinction risk, at least at the population level.

Indirect effects would, similar to the arguments on speciation (Althoff et al. 2014), result from changes in organismal biology or geography (e.g., species range size) that reduce extinction probability. Those indirect changes would consist of a secondary effect resulting from the evolutionary changes directly related to the interaction between plants and herbivores. For example, the acquisition of a new chemical defense might allow plants to expand their geographical range, a condition that has been associated with lower extinction probability, although the causal direction might be hard to establish or even act in both directions (Foote et al. 2008).

The importance of those direct and indirect effects on extinction and speciation might be difficult to infer or predict, but it might be worth exploring the possibility that it is related to the asymmetry on how insect and plants might affect each other's diversification according to the escape-and-radiate scenario (Ehrlich and Raven 1964; Janz 2011). Although the effect of plants on insect diversification might be direct because they offer different hosts on which the subsequent herbivore diversification might occur, the effect of insects on plants is rather indirect because it is the absence of insects that would in theory allow plants to radiate (Ehrlich and Raven 1964; Janz 2011; Hembry et al. 2014). We see no clear expectation of whether increases in diversity due to either an increase in speciation or decrease in extinction might preferentially operate in plants and herbivores, but the asymmetry described above and the neglected effect through extinction might serve as motivation for further theoretical and empirical work. For example, it is possible that the "escape" from herbivory might lead to direct effects on lowering plant extinction due to lack of population suppression effects, and indirect effects on plant speciation due to increased opportunities for allopatric speciation due to the extended range. Alternatively, it is possible that the herbivore's ability to use a new suit of host-plants might have direct effect on herbivore speciation by allowing specialization on slightly different host-plants, and an indirect effects on extinction by allowing largest ranges if the access to new hosts represents an increase in diet breath.

Measuring extinction rates will be particularly challenging because molecular phylogenies have shown to be limited when trying to infer deep time diversification dynamics (Louca and Pennell 2021). In that respect focusing on tip rates might be more promising (Louca and Pennell 2021), and in fact suffice for the challenge. The fossil record, which in theory would be a more direct source to infer extinction rates, is usually incomplete, limiting detailed inference at the species level to few lineages, but could also be explored. This might indeed, and perhaps not surprisingly, be part of the reason why such processes might have been neglected in the past. While the challenge is big, we suspect that the study of herbivore-plant interactions should prosper with this endeavor.

The escape-and-radiate coevolution hypothesis as "a bridge" from micro to macroevolution

Another important aspect of E&R paper is that it nicely exemplifies the difficulty of bridging micro and macroevolution. Although the original paper lacked an explicit mechanism, it prompted the discussion on how population/microevolutionary mechanisms, in particular the evolution of reproductive isolation would result in an increase in speciation rate (or more correctly, the increase in net diversification rate) as predicted by the escape-and-radiate hypothesis (Janz 2011; Althoff et al. 2014; Hembry et al. 2014). Although we do not doubt the importance of reproductive isolation to explain differences in speciation rate, there has been a growing sense that other mechanisms might be relevant when one is trying to bridge the gap between micro and macroevolution (Harvey et al. 2019). For example, a comparative study of birds and flies suggested that the rate of evolution of reproductive isolation (measured within species) is not associated with the rate of speciation in a phylogenetic comparative framework, suggesting that other mechanisms might be at play (Rabosky and Matute 2013).

One excellent paper that lays out those mechanisms is the paper by Dynesius and Jansson (2014). Under their framework (see figure 3) three different population/microevolutionary mechanisms are at play: population splitting, population persistence, and speciation duration, which might be defined slightly differently according to the species definition used (Dynesius and Jansson 2014). In the case of the biological species concept (which might be seen as the most frequent concept adopted for microevolutionary studies interested in the escape-and-radiate hypothesis), the inverse of speciation duration can be described as the rate of evolution of reproductive isolation. Under this framework it is the combination of those three processes that will produce what we measure at the macroevolutionary scale, the speciation rate (figure 3).

Lineages that quickly evolve reproductive isolation (those with shorter speciation duration) would expect to show higher speciation rates but if those newly formed species do not last long enough (lower persistence), then we should not expect speciation rate to be high when measured at a macroevolutionary scale (Harvey et al. 2019; see also figure 3). This argument was also presented by Rosenblum et al. (2012) which suggested that the low persistence of "incipient species" would explain the discrepancy between rates of speciation measured at different time scales (young vs old radiations) or using different approaches (theoretical models vs fossil record and phylogenies). Those authors propose the ephemeral speciation model where species emerge fairly quickly, but most of those do not last long. Similarly, Futuyma (1987, 2010) suggested that long term stasis seen in the fossil record could be due to what he called the "ephemeral divergence" hypothesis where populations that diverge from the ancestral stock eventually merge back together to the ancestral population or go locally extinct. In that sense lower population persistence prevents new forms and species to emerge not only affecting morphological evolution but also speciation rate (Dynessius et al. 2014).

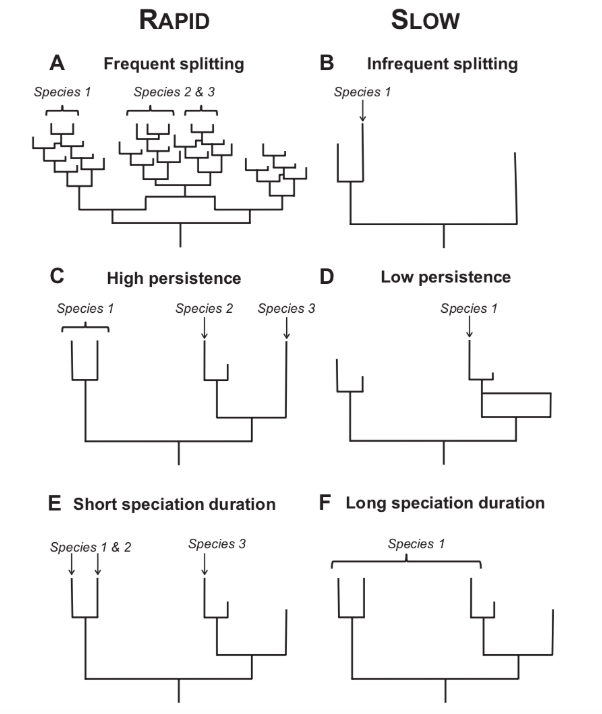

Figure 3: Schematic proposed by Dynesius and Jansson (2014) to illustrate the different population/microevolutionary level mechanisms that might eventually affect speciation rate measured at the macroevolutionary scale, namely splitting (panels A and B), persistence (panels C and D) and speciation duration (panels E and F). Phylogenies contain extant and extinct populations and species. Scenarios shown in panels A, C, E would lead to higher speciation rates than their corresponding panels B, D, F. We advocate the study of herbivores and plants to consider these different hypothetical effects when studying the macroevolutionary effects of such interactions. Figure reproduced from Dynesius and Jansson (2014) with permission.

In most microevolutionary studies, related or not to the escape-and-radiate hypothesis, the typical population/microevolution level mechanism studied is the evolution of reproductive isolation, and to a lesser extent, the rate of population splitting. We note that most literature on herbivore-plant interaction, and in particular those directly related to the escape-and-radiate hypothesis, do not explicitly consider how coevolution might separately affect the rate of evolution of reproductive isolation, population splitting and population persistence. Fewer exceptions exist, but even those (e.g. Althoff et al. 2014; Hembry et al. 2014) typically neglect population persistence or do not treat reproductive isolation and persistence separately. Hembry et al. (2014) and Thompson (2005) discussed how coevolution might "*make geographical isolation more probable*", which in the context of figure 3 would be related to changing the rate of population splitting. Similarly, Althoff et al. (2014) allude to the splitting mechanism to discuss how coevolution might lead to limited gene flow between different populations and hence influence the evolution of reproductive isolation. Although their argument is centered in the evolution of reproductive isolation, ideas related to the rate of splitting are there. In fact, Althoff et al. (2014) suggest that we have evidence that coevolution can lead to divergent evolution (and hence eventually rate of splitting), but the effects of such divergent evolution on reproductive isolation is not well understood or documented. Although previous work has touched the aspect of splitting, we are not aware of studies that have explicitly considered all three mechanisms (splitting, reproductive isolation and persistence) simultaneously. In particular, most mechanistic discussions that succeed the Ehrlich and Raven paper (1964) have, for the most part, neglected the effect of coevolution on population persistence, and according to Suchan and Alvarez (2015), persistence has never been empirically tested in the context of herbivore-plant interactions.

If lower persistence of incipient species is indeed a common phenomenon (Futuyma 2010; Rosenblum et al. 2012; Dynessius et al. 2014), and if coevolutionary diversification preferentially acts through population persistence, then as pointed in a broader context, speciation rates measured at macroevolutionary scale might be more influenced by persistence than by the evolution of reproductive isolation *per se* (Rosenblum et al. 2012; Rabosky 2013; Harvey et al. 2019). It might therefore be interesting to revisit the biological mechanisms proposed to underlie the escape-and-radiate hypothesis and discuss, as pointed out by Dynessius et al. (2014) in a broader context, how coevolution could affect separately the splitting rate, reproductive isolation, and in particular, population persistence.

We argue that using this framework might turn the study of herbivore-plant interaction, and more specifically the escape-and-radiate hypothesis, into a powerful tool/framework to help us bridge the micro and macroevolution gap. There is already the perception that linking population and microevolutionary processes to macroevolutionary patterns should enhance our understanding on how coevolution could act as an engine of diversification (Althoff et al. 2014; Thompson 2005), there are already a reasonable amount of data and interest in either micro and macroevolutionary aspects of coevolution (e.g. see reviews and references therein by Althoff et al. 2014; Maron et al. 2019; Hembry and Weber 2020), there are some insect-plant systems that are amenable to experimental studies (e.g., Gaba and Ebert 2009), and we have some knowledge of the underlying genetic mechanisms (e.g., Xia et al. 2021).

Althoff et al. (2014) conclude their very insightful paper suggesting that three different criteria must be met before a solid inference on the role of coevolution on diversification could be made: "*First, coevolution must be important in facilitating divergence among populations within a coevolving species. Second, coevolving traits should influence reproductive isolation, either directly or indirectly, among diverging populations. Finally, coevolving lineages should have higher net diversification rates than non-coevolving lineages.*" We agree with those criteria but given recent advances in both micro and macroevolution fields, we feel inclined to add a few more. We argue that coevolutionary diversification might happen when coevolution also changes population persistence or extinction dynamics. In that sense coevolution might still have a strong effect at macroevolutionary scales even if it does not affect the rate of evolution of reproductive isolation or population splitting. Further studies on population level consequences of herbivore-plant interactions will be particularly valuable to evaluate the idea that coevolutionary diversification acts through extinction dynamics, either of fully fledged species or of incipient ones. Inferences gathered at the population/microevolutionary level, ideally of the three processes discussed here, should then be compared, in a similar manner as that done by Rabosky and Matute (2013), ideally to both speciation and extinction rates measured at the macroevolutionary scale.

Conclusion

After almost 60 years of its publication, E&R paper is still a major source of insights and venues of research to the study of ecological interactions, and in particular of insect herbivores and their host plants. By proposing a macro-coevolutionary hypothesis for the diversification of two dominant groups of organisms (in terms of species richness), E&R ideas impacted several different lines of research, from genetic controls of traits mediating interactions to ecological networks, to the natural history of plants and associated herbivores to macroevolutionary dynamics of interacting clades. The inherent complexity of the coevolutionary process that was tackled by the E&R paper called for the combination of multiple processes and patterns operating at different spatial, temporal, and organizational scales. Because of that complexity, to attain some of the future goals proposed in this perspective, we suspect that a multi-disciplinary approach will be required. However, in that respect, we envision that the research centered around the elements of the escape-and-radiate coevolution hypothesis might eventually help us to better understand how the genetic controls of species interactions may shape ecological networks that are influenced and influence the macroevolutionary dynamics of interacting groups of organisms. We think that the integration of these three different fields may eventually help us to bridge the micro and macroevolutionary gap, creating an unified theoretical map for how coevolution affects the diversity of life.

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