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1 **Unraveling coevolutionary dynamics using ecological genomics**

2

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32 **Abstract (101 words)**

33 Coevolutionary interactions, from the delicate co-dependency in mutualistic interactions to the  
34 antagonistic relationship of hosts and parasites, are a ubiquitous driver of adaptation. Surprisingly,  
35 little is known about the genomic processes underlying coevolution in an ecological context.  
36 However, species are composed of genetically differentiated populations that interact with  
37 temporally variable abiotic and biotic environments. We discuss the recent advances in  
38 coevolutionary theory and genomics as well as shortcomings, to identify coevolving genes that  
39 take into account this spatial and temporal variability of coevolution, and propose a practical guide  
40 to understand coevolution in a more realistic manner using genomic and phenotypic data.

41

42

43 **Keywords:** coevolution, population genomics, association mapping, species interaction, ecology,  
44 adaptation.

## 45 **What we know and do not know about coevolution**

46 Species involved in symbioses have the potential to shape each other's evolutionary trajectory  
47 through reciprocal selection and adaptation, *i.e.*, they have the potential to coevolve. **Coevolution**  
48 between two or several species is a fundamental mechanism shaping the organization and diversity  
49 of life [1–5]. Surprisingly, we know little about the genomic processes underlying coevolution,  
50 particularly in an ecological context. Indeed, genomic studies of coevolution have predominantly  
51 focused on only one of the partners, thus telling only half of the story (but see [6–9]). Furthermore,  
52 most genomic studies of coevolution have focused on single populations [10–18] (but see [6,9]).  
53 However, species are composed of genetically differentiated populations embedded in a network  
54 of interactions with complex and temporally varying abiotic and biotic environments. Local  
55 populations of species coevolve over short and long-time scales in complex **habitats**. Thus, the  
56 coevolution of two (or more) species is expected to vary across space and time, and depends on  
57 the cumulated effects of ecological and evolutionary processes acting within and among  
58 **populations**. So far, the large set of population genomics and statistical association tools (applied  
59 to model and non-model species) available for understanding the evolutionary processes involved  
60 in species diversification and adaptation [19–21] have seldom been used to investigate the genes  
61 underlying coevolution [22].

62 We argue that the lack of *ad hoc* inference and statistical approaches to study the  
63 complexity of coevolution at appropriate temporal and spatial scales hampers our understanding  
64 of the processes involved in coevolution, and prevents the detection of genes underlying  
65 coevolution. This theoretical lag can be partly explained by the strong divide between the  
66 theoretical predictions of the ecological dynamics of coevolution over short time scales, which do  
67 not imply genomic perspectives [23–25], and the theory of the genomic consequences of

68 coevolutionary dynamics which would benefit from a deeper consideration of the ecological  
69 context (Boxes 1 and 2).

70         Here, we first summarize the main theoretical and empirical advances that allow the  
71 identification of the main processes shaping coevolution. We emphasize that understanding both  
72 the demographic and adaptive processes over space and time is critical for identifying the genes  
73 involved in coevolution. Second, we review the recent advances in coevolutionary theory, as well  
74 as in population genomics and association mapping methods (*i.e.*, genome-wide association  
75 studies, GWAS, and gene-environment-wide association studies, GEAS), that have proving useful  
76 for understanding coevolutionary dynamics and the genes involved. We also discuss the need to  
77 develop suitable statistical methods to address coevolution in a more realistic manner (*i.e.*, in its  
78 complexity) using genomic and phenotypic data. In a third part, we provide a practical guide (Box  
79 3) for studies of coevolution using genomic data, that aim to determine whether adaptations in  
80 interacting species truly stem from reciprocal selection [4,5,15,16]. We focus on host-parasite  
81 systems involving two species because data and theoretical expectations are primarily available  
82 for these systems. We believe that the theoretical and empirical developments currently tested on  
83 host-parasite systems, and presented below, could be applied to other symbiotic systems involving  
84 two or more species.

85

### 86 **The three main processes shaping coevolution across space**

87 Theory identifies three processes that shape coevolution (Box 1, Figure 1). The first one is  
88 **demographic processes** [3,26,27] (Figure 1a), which include genetic drift affecting allele  
89 frequencies within populations, gene flow between populations and **metapopulation** dynamics  
90 (local population extinction and recolonization) [3]. In addition, interacting species may have

91 different population structures, different levels of gene flow and be differentially affected by local  
92 (abiotic) environments. It is therefore crucial to consider the population structure of each  
93 interacting species when studying coevolution [28,29]. At the metapopulation level, populations  
94 of interacting species can also share elements of a past demographic history (*e.g.*, common post-  
95 glacial expansion), which are relevant for understanding the processes of coevolution. Second, the  
96 outcome of inter-specific interactions, *i.e.*, the genotype-by-genotype interactions (referred to as  
97 GxG hereafter, Figure 1b) defines directly the parameters of coevolution (strength of coevolution,  
98 disease severity, virulence of the parasite, fitness costs of resistance or infectivity). Third, within  
99 and across **habitats**, spatially variable selection, *i.e.*, the **selection mosaic**, is characterized by the  
100 heterogeneity in biotic and abiotic interactions. This selection mosaic can, in its simplest form, be  
101 represented by a spatial matrix of **coevolutionary coldspots and hotspots** defined by the presence  
102 of one species (single species evolution) or both interacting partners (coevolution), respectively.  
103 For instance, in the mutualism between fig trees and fig wasps, there are only hotspots as fig trees  
104 and fig wasps fully depend on each other. The spatial heterogeneity has also the potential to  
105 generate more complex patterns: genotype-by-genotype-by-environment interactions (referred to  
106 as GxGxE hereafter, Figure 1c). This means that the strength and speed of coevolution can vary  
107 across localities within and among habitats (Figure 1c). In other words, the importance of  
108 coevolution to the overall evolution of a population can vary across space. Low levels of gene flow  
109 can result in asynchrony of the **coevolutionary dynamics** between populations while high levels  
110 of gene flow may homogenize gene pools and synchronize coevolutionary dynamics across space  
111 [24,30].

112           Given the complexity of variable selection and demographic processes (Figure 1d), it is  
113 crucial to assess the relative importance of demographic (*i.e.*, **effective population size**  $N_e$  and

114 gene flow) *vs.* adaptive (*i.e.*, GxG, GxE and GxGxE) processes in driving coevolution over space  
115 and time. Below, we summarize studies which provide first glimpses into coevolutionary  
116 dynamics, that rely on two main approaches: 1) population genomics inference methods that take  
117 into account demographic processes to detect GxG interactions, and 2) genome-wide association  
118 studies (GWAS and GEAS), which provide insights into GxGxE interactions. We also discuss new  
119 or improved statistical methods in these fields that allow the study of more realistic, hence more  
120 complex, scenarios.

121

122 **How have population genomics and genome-wide association studies provided an insight into**  
123 **the dynamics of coevolution?**

124 **a. On demographic processes and co-spatial genetic structures**

125 Inferring the demographic history of each species in each population and the spatial genetic  
126 structure of each species is important to draw accurate conclusions regarding the strength of  
127 coevolution [29]. This can be achieved using a population genomics approach based on a large set  
128 of genetic markers (preferably genome-wide polymorphism data) to simultaneously estimate the  
129 **effective population size ( $N_e$ )** and its variation over time and space, the population genetic  
130 structure and the extent of gene flow among populations of each species in interaction. The  
131 population structure of coevolving species has been characterized only in a few model systems.  
132 One of these is the anther smut fungus *Microbotryum violaceum* and its host, members of the plant  
133 genus *Silene* (specifically *S. latifolia*). These species show strong spatial **genetic co-structure**,  
134 probably because the pollinator of *Silene* is responsible for both the long-distance dispersal of the  
135 smut fungus and long-distance gene flow in *Silene* [28,31]. In newts (*Taricha granulosa*) that are  
136 preyed on by garter snakes (*Thamnophis sirtalis*), the levels of newt (prey) toxin and garter snake



137 (predator) resistance are tightly matched across the landscape. Although predator resistance is  
138 geographically structured according to signatures of **local adaptation** to prey, levels of prey toxin  
139 are structured following neutral population divergence [32]. This later study suggests that neutral  
140 processes, including gene flow, rather than reciprocal adaptation explain most of the phenotypic  
141 variation of the two interacting species observed across the landscape. Two other studies that  
142 investigated spatial co-structure of mutualist interactions [33] also detected spatial structure in  
143 either the host or the symbiont, but no spatial co-structure: 1) in [34], genetic differentiation in the  
144 legume *Medicago lupulina* was roughly concordant with the geographic turnover of its N-fixing  
145 bacterial symbionts *Ensifer* but only at the genus level; 2) in [35], the leafcutter ant *Atta texana*  
146 showed variable levels of congruence with its two main fungal symbionts, most likely because the  
147 strength of drift and gene flow differs between the fungal partners. There is a need for additional  
148 studies of interacting species to quantify the importance of life-history traits such as host and  
149 parasite life span, parasite transmission, dormancy, selfing or clonal reproduction in shaping the  
150 spatial co-structure and the coevolutionary dynamics within and between populations. New  
151 methods [36,37] can be used to infer divergence time, rate of gene flow and  $N_e$  (and its variation  
152 in time, Box 2), while taking into account variable rates of gene flow along the genome. Such  
153 inferences are important for defining a neutral threshold (*i.e.*, the consequences of demography)  
154 in order to identify the genes under selection in host and parasite genomes. Population genomics  
155 inference methods should also be developed to compare demographic histories, spatial structures  
156 and gene flow in several species simultaneously (see recommendations in [19]; Box 3).

157

158 **b. Inference of local selective process of coevolution *per se* (GxG)**

159 Classical models that predict coevolving loci within populations rely on the identification of  
160 signatures of selective sweeps (*i.e.*, arms race) or balanced polymorphisms (*i.e.*, trench warfare  
161 dynamics, also called Red Queen dynamics) in the genomes [2,38] (Box 1). Few methods take into  
162 account the role of polygenic traits in coevolution [25,39,40]. Furthermore, the theoretical  
163 expectations regarding loci of major effect have been recently challenged by studies that take  
164 demographic processes (*e.g.*, genetic drift) into account [41–45]. Specifically, trench warfare  
165 dynamics are predicted to be less likely than arms race dynamics when local population sizes are  
166 small (Box 1) [43–45]. This seems particularly true when population sizes vary over time due to  
167 eco-evolutionary feedback [43,44,46]. Nevertheless, trench warfare dynamics may occur in local  
168 populations as alleles from asynchronized populations are reintroduced by gene flow [47] or  
169 because of spatial heterogeneity among populations [48,49]. The signatures of trench warfare or  
170 arms races, especially when these dynamics occur over a brief period of time, are not necessarily  
171 detectable in the genome [43,45]. Theory also predicts that polymorphism signatures of  
172 coevolution within a population, especially signatures of selective sweeps due to arms race, are  
173 more likely to be detected in parasite than in host genomes, but only if parasites show sufficiently  
174 high rates of recombination [41]. Recently, host and parasite polymorphism data were jointly  
175 analyzed using a new framework: approximate Bayesian computation (ABC hereafter). This  
176 framework was used to infer the type of dynamics at coevolving loci, as well as detect genes in  
177 coevolution and infer the parameters of coevolution (disease severity, effectiveness of resistance,  
178 etc.) [22]. This is an interesting new tool for understanding the dynamics of coevolution, but it also  
179 has drawbacks as it requires repeated sampling in space and time in order to infer the main  
180 parameters that define coevolution, namely, the reduction in host fitness due to infection [48,50].

181 Future approaches to identify coevolving genes from genomic data need to move beyond the  
182 analysis of single populations and the focus of coevolutionary dynamics only from major loci.  
183 New quantitative models could be based on phenotypic-matching and phenotypic-difference  
184 approaches and should take population heterogeneity into account (Box 1). At present, methods to  
185 detect genes under selection across populations rely on the identification of population  
186 differentiation outliers (*e.g.*,  $F_{ST}$ ,  $XtX$ ). Statistical thresholds in such scans need to account for the  
187 neutral spatial structure and demographic history of each species. New approaches can provide  
188 more explicit demographic models based on the inferred co-structure and co-demographic history  
189 of coevolving pairs of species (Box 2).

190

### 191 **c. Inference of spatially heterogeneous selection (GxGxE)**

192 Selection pressure from abiotic and biotic conditions (*e.g.*, temperature, humidity, food sources,  
193 competition) can be highly variable over space and time [3]. Hence, in addition to coevolution  
194 depending on variation in the host and the parasite (GxG), spatial variation in species interactions  
195 can be affected by other sources of variation leading to GxGxE (Figure 1). The contribution of  
196 environmental conditions to overall selection depends, amongst other factors, on the closeness of  
197 the interaction. Intracellular parasites, for instance, are nearly exclusively exposed to selection  
198 pressures imposed by the host, although parasites of invertebrates and plants are also indirectly  
199 exposed to the outside environment since it determines the host's temperature. By contrast,  
200 parasites and mutualists with extended free-living periods face significant selection pressures other  
201 than factors associated with host resistance [4,51]. Parasites of annual crops (and other annual  
202 plant species) must survive extended periods in a host-free environment before the host becomes  
203 available. Hence, tolerance to desiccation, solar radiation and possibly alternative modes of

204 nutrition that are independent of a host may be important [52]. Some parasites, such as fungal  
205 pathogens or aphids, also rely on an alternative host to complete their life cycle [53,54]. For  
206 instance, the devastating stem rust pathogen of wheat requires an alternative host, barberry, for  
207 sexual reproduction, thus adding further host-dependent selection on the parasite. Crop pathogens  
208 also show local adaptation to climatic conditions and the presence of chemicals (*i.e.*, fungicides  
209 applied to protect crops, see below).

210 GxGxE can generate local adaptations and potentially constrain the evolution of  
211 exploitative strategies (*e.g.*, pathogenicity) and in turn alter the coevolutionary dynamics.  
212 Furthermore, even though a trade-off between traits in the host (or parasite) can occur in the  
213 absence of environmental variation, the magnitude and direction of the trade-offs can show large  
214 variance across **habitats**, and thus potentially shed light on the genetic bases of GxGxE  
215 interactions. For instance, fungicides sprayed on crops select for pathogen populations with  
216 reduced growth rates in absence of fungicides [55]. Hence, fungicides impose a shift towards a  
217 new trait optimum. Pathogen populations often vary in such trait optima [55]. GWAS are well  
218 suited to identify loci with genetic variants associated with these trait variations [56]. In a major  
219 wheat pathogen, a systematic investigation of environment-dependent trade-offs among adaptive  
220 traits across the life-cycle revealed significant constraints [57]. Importantly, adaptation to different  
221 hosts showed trade-offs with environmental adaptation, in this case to temperature and fungicides  
222 [57]. Although traits related to pathogenicity on different host genotypes were largely correlated,  
223 the pathogen faced a specific trade-off between killing host plant tissue necessary to acquire  
224 nutrients and producing spores for dispersal. The exact molecular mechanisms underlying these  
225 trade-offs remain largely unknown. In a recent pioneering study, Roberts *et al.* [58] demonstrated  
226 that in the lepidopteran species (*Plodia interpunctella*) and its DNA virus (PiGV), variation in the

227 architecture of resistance of the host to PiGV depends on available resources (*i.e.*, the abiotic  
228 environment). GWAS in controlled conditions can be used to reveal the genetic basis of the trade-  
229 offs between coevolving genes but also between coevolving genes and other metabolic pathways,  
230 while providing empirical data for the population genomic analyses. Furthermore, GEAS studies  
231 can identify genes and alleles of importance in GxGxE interactions, while taking as co-variables  
232 environmental data (*e.g.*, climate) across habitats [59]. However, in all association studies,  
233 distinguishing the effects of mutations that are directly responsible for the phenotype from  
234 correlated mutations (*i.e.*, from linkage disequilibrium) remains an issue [60]. We argue that  
235 systematic investigation of GxGxE will prove crucial for deciphering the genetic architecture of  
236 trade-offs across **habitats**, and for predicting the coevolutionary trajectories of interacting species  
237 across heterogeneous landscapes (Box 3, Figure 2).

238

### 239 **A framework to decipher the genetic bases of coevolution**

240 Advances in technology and statistical approaches will open new avenues understanding  
241 coevolution from an ecological and genetic perspective. In the near future, methods to jointly  
242 analyze genomic data from hosts and parasites across **populations** and **habitats** should become  
243 available. We propose a practical guide for carrying out such analyses based on existing methods  
244 (Box 3, Figure 2). Note that we focus on host-parasite interactions because these are the best  
245 studied systems (but see [6]). However, research on coevolution is increasingly trying to  
246 understand how networks rather than just pairs of interacting species coevolve [1–5]. The next  
247 challenge will be to develop the statistical and theoretical toolbox that can integrate population  
248 genomics and association mapping in different ecological settings, *i.e.*, that can integrate a large  
249 parameter space with several species at the community level while retaining statistical power.

250 Solving these issues will go a long way in addressing the question of whether adaptation in  
251 coevolving species truly stems from coevolution [4,5,25,26], and will improve our understanding  
252 of the evolution of complex communities [1,4,61–63].

253

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455

456

457 **Highlight**

- 458 ● Coevolution is a fundamental process shaping species interactions and communities.
- 459 ● Coevolution has been mostly studied experimentally as an isolated process involving local  
460 reciprocal selection between two species. However, species are composed of genetically  
461 differentiated populations across space in constant interaction with dynamic abiotic and  
462 biotic environments. Coevolution is therefore a dynamic equilibrium.
- 463 ● The genes and genomic processes underlying the complexity of coevolution over time and  
464 space are still poorly known.
- 465 ● A range of new theoretical developments, technological advances and empirical  
466 approaches now allow coevolutionary dynamics to be investigated with genomic data from  
467 interacting species.
- 468 ● Recent advances in population genomics and genome-wide association studies will enable  
469 us to better understand the genetic basis of coevolutionary dynamics.

470

471 **Outstanding questions**

- 472 ● What and how many genes are involved in coevolution, *i.e.*, what is the genetic architecture  
473 underlying coevolution?
- 474 ● What are the evolutionary trajectories of these genes (type of selection) within and between  
475 populations and habitats, and can these be inferred from patterns of polymorphism?

- 476       • Are the same genes/types of genes involved across 1) host or parasite species, 2) habitats  
477       of a given symbiont species (host or parasite), or 3) antagonistic or mutualistic systems  
478       from the same geographic location (trophic network)? What is the genetic basis of trade-  
479       offs in host and parasite populations?
- 480       • How can the theory and genomic tools developed for the study of two-species interactions  
481       be adapted to multi-species interactions at the community level?

482

### 483 **Glossary**

484 **Coevolutionary dynamics:** dynamics of genotype/trait/allele frequencies in interacting species  
485 due to the reciprocal nature of coevolution.

486 **Coevolutionary hotspots/coldspots:** locations where interspecific interactions are strong and  
487 reciprocal are defined as hotspots, whereas areas where population interactions are asymmetric or  
488 nonexistent are defined as coldspots.

489 **Genetic co-structure:** statistical congruence between the population genetic structures of  
490 interacting species.

491 **Demographic processes:** include population size fluctuations over time and space, which  
492 influences the variation in **effective population size ( $N_e$ )**, and gene flow among populations.  
493 Changes in  $N_e$  (the demography history of a population) and gene flow influence the efficiency of  
494 selection and thus the strength of coevolution.

495 **Ecological dynamics:** changes in population size (or population density), here in the context of  
496 eco-evo feedbacks in host and parasite populations.

497 **Effective population size ( $N_e$ ):** the number of individuals that effectively participate in  
498 producing the next generation.  $N_e$  determines the rate of change in the composition of a



499 population caused by genetic drift, *i.e.*, the random sampling of genetic variants in a finite  
500 population.

501 **Habitat:** the set of local abiotic and biotic conditions experienced by one or several populations  
502 in a given geographic area.

503 **Gene flow:** the migration of individuals, and thus of genes/alleles, between populations/demes.

504 **Local adaptation:** In spatially heterogeneous environments, evolution can lead to the adaptation  
505 of populations to their local environmental conditions. Pattern of local adaptation occurs when the  
506 mean fitness of a population in their home environment is higher than the mean fitness of  
507 populations from elsewhere [64].

508 **Metapopulation:** populations connected by gene flow. Individual populations may go extinct and  
509 new populations may be established by migrants.

510 **Population:** a group of individuals who are more genetically similar to each other than they are to  
511 individuals outside the subpopulation, as a result of genetic drift, migration, mutation, and  
512 selection. Also called “deme” in the metapopulation framework, and often assumed as a panmictic  
513 group inferred from Bayesian inference methods in population genomics studies [65–67].

514 **Selection mosaic:** spatial variation in the strength of coevolution (hot- and cold- spots) among  
515 interacting species due to spatial variation in the biotic and selective pressure.

516 **Box 1. Theoretical foundation of the genetic basis of coevolution**

517 Theory predicts that the coevolutionary dynamics of allele frequencies in antagonistic interactions  
518 are situated between two extreme scenarios [2,22,38]. In “arms race” dynamics, alleles at  
519 coevolving loci are repeatedly fixed, typically leading to signatures of positive selection. “Trench  
520 warfare” dynamics, in which several alleles at coevolving loci are stably maintained, typically  
521 result in signatures of balancing selection. The genomic architecture of coevolution, *i.e.*, the  
522 number, location, and effect of the genes involved, has been considered to be either Mendelian or  
523 quantitative [25]. In Mendelian models, the arms race occurs at one or few major genes. An arms  
524 race in a quantitative trait set up corresponds to the phenotypic difference model [25]. The  
525 quantitative model equivalent in trench warfare is the phenotypic matching model [25]. While  
526 these expectations provide a rationale for conducting selection scans on genes of major effect, the  
527 theoretical framework is ill-suited for making inferences on the genomic footprint of coevolution  
528 in an ecological context. First, coevolutionary dynamics are affected by ecological and  
529 evolutionary factors [43,44,46,68]. This means that demographic processes due to finite population  
530 size [45] and changing population sizes due to eco-evolutionary feedback need to be accounted for  
531 when analyzing genome-wide patterns of polymorphism [43,44,46,68]. Indeed, it has now been  
532 shown convincingly [44,48] that (negative indirect) frequency-dependent selection generated by  
533 host-parasite coevolution in itself does not guarantee the occurrence of long-term trench warfare  
534 dynamics [44,45]. Second, the complex and heterogeneous spatial structure of interacting species  
535 and the variable rates of gene flow and recombination across the genome need to be accounted for  
536 when detecting selection because these change the expectations regarding the footprints of  
537 coevolution (signatures of arms race or trench warfare) (reviewed in [22]).

538

539 **Box 2. Co-demographic processes in host-parasite interaction**

540 Coevolution is characterized by a variation in the hosts' and the parasites' fitness over time, which  
541 generates variation in population size within and between populations of a metapopulation (Figure  
542 1 and Box 1, [41,44,46,47,69]). Within a population, there is covariation in host and parasite  
543 population sizes over short timeframes due to the eco-evolutionary feedback (Figure 1), which is  
544 referred to as the co-demographic history [47]. The strength of the eco-evolutionary feedback is  
545 determined by the environmental effect on infection, epidemiology and local density-dependent  
546 regulation [69]. Such rapid eco-evolutionary changes in population size (the effective population  
547 size,  $N_e$ , of both species) are observable using genomic data sampled in a time series, and are thus  
548 likely to be relevant for predicting host-symbiont genome coevolution [58]. At the metapopulation  
549 level, field studies show that *Silene* or *Plantago lanceolata* populations exhibit strong  
550 metapopulation dynamics with frequent host and/or parasite extinction-recolonization influencing  
551 parasite persistence and population sizes [52]. To reveal these co-demographic events, a large  
552 dataset obtained across space and time is necessary; however, obtaining this may be difficult for  
553 many systems. The approach proposed in [68] may allow the fast reconstruction of the  
554 coevolutionary dynamics of interacting species using sequence data of species amenable to  
555 laboratory coevolution experiments or for which data can be sampled over a sufficient number of  
556 generations across several coevolutionary cycles. The sampling time scale is then defined by the  
557 generation time of hosts and parasites. For instance, time sampling is more amenable in annual or  
558 multi-annual species than in perennials. In the future, genome-wide statistical methods should  
559 allow the inference of coevolving host and parasite allele trajectories across populations and  
560 habitats using samples at different time points, while taking into account for the past demography  
561 and spatial structure of each species and their co-demographic history. This would allow us to

- 562 decipher the bases of GxGxE interactions using genomic scans of selection at a high spatial and
- 563 temporal resolution (see above).

564 **Box 3. A practical guide of the ecological genomics approaches for investigating coevolution.**

565 We propose the following steps for carrying out in-depth coevolutionary studies (Figure 2):

566 **1) Hierarchical sampling:** sample infected (and uninfected if present) hosts and their infecting  
567 parasites in several **populations** from the same **habitat** and in several different **habitats**. The  
568 information regarding which parasitic individual infects which host should be kept.

569 **2) Sequencing:** sequence individuals of both host and parasite and perform read mapping and  
570 variant calling. Ideally, high-quality reference genomes are available for analyzing gene families.  
571 Sequencing can involve full genomes or sequence capture of a few thousand genes including  
572 candidates for immunity, resistance and pathogenicity.

573 **3a) Inferences of the demography and population structure for each species.** The variance of  
574 migration rate can be compared to information from recombination maps when available (or by  
575 simultaneous modelling of demographic history and inference of recombination maps using the  
576 iSMC method on full genome data [70]). Indeed, correlation between the rate of gene flow and  
577 that of recombination depends on selection at introgressed genes (adaptive *versus* maladaptive,  
578 across populations and habitats). We also suggest using full genome data to test for correlation  
579 between the demographic history of host populations and that of parasite populations using the  
580 comparative pairwise sequentially Markovian coalescent, C-SMC method [71]. ABC [72] and  
581 machine learning methods [73] can be used to infer the demographic history and the spatial  
582 structure parameters for more complex scenarios.

583 **4a) Selection scans:** apply scans using the neutral demographic model and inferred spatial  
584 population genetic structure to set statistical thresholds. It is possible to run selection scans on host  
585 (infected and non-infected) and parasite samples within a population, on a pool of populations  
586 from the same habitat and on all populations from different habitats. This makes use of the power

587 of hierarchical sampling to detect selection based on  $F_{ST}$  [74],  $XtX$  [75], or dimension reduction  
588 (*e.g.*, principal component analyses [76] or genotype matrices) methods as well as on classic  
589 selective sweep or balancing selection tests.

590 **3b and 4b) Sampling over time:** with appropriate sampling, it is possible to test the co-  
591 demographic history of hosts and parasites based on the site frequency spectrum of hosts and  
592 pathogens at different time points [68]. The number and periodicity of the time sampling depend  
593 on the life cycle of the host and the parasite. For instance, time sampling is more amenable in  
594 annual or multi-annual species than in perennials. Based on simulations of neutral background  
595 changes in allele frequencies, it is possible to study genes under coevolution with outlier allele  
596 frequencies over time [77].

597 **5a) Co-genomics:** using the full genomes or sequence capture data from hosts and parasites, we  
598 suggest carrying out co-GWAS for organisms for which it is doable [26,78], from which cross-  
599 species association indices can be used to identify genes under significant association [20,50],  
600 followed by the inference of coevolutionary parameters at major loci [74]. If experiments are  
601 possible, performing all possible pairwise infection tests and using co-GWAS is very powerful to  
602 identify the genes underlying the interaction [40]. It is advisable to perform co-GWAS under  
603 different environmental conditions to account for GxGxE effects, or use GEAS to link genetic  
604 variation of hosts and parasites to environmental variables [59], *e.g.*, climate.

605 **5b) Functional validation:** if controlled experiments are possible, the number of candidate loci  
606 involved in coevolution can be obtained from **co-expression analyses** (joint RNAseq [79] or  
607 proteomics) of host and symbiont samples. Co-expressed genes can be compared to those  
608 identified by co-GWAS and selection scans. Cross-species eQTL mapping combined genomes and  
609 gene expression can identify polymorphisms in the host genome affecting parasite expression, and

610 *vice versa* [80]. New tools to determine protein structure (AlphaFold and RoSetta for instance  
611 [81,82]) may also deepen our insights into the molecular basis of protein interactions and  
612 coevolution. Functional assays to validate these candidate genes and proteins at the population  
613 level in the host and the parasite is the final step that can be done together with population  
614 genomics approaches.  
615

616 **Figure 1. Major factors underlying coevolutionary dynamics in an ecological context.** For  
617 simplicity, we focus on host-parasite (h-p) coevolution [3,83]. Species that interact in a given  
618 geographic area (*i.e.*, **habitat**) are collected multiple times across a spatial gradient. Gene flow  
619 occurs among host or parasite populations and habitats. The three processes determining  
620 coevolutionary interactions in an ecological context using a population genomics lens are: **a.** the  
621 demographic processes occurring within and between populations; **b.** the process of coevolution  
622 (GxG) in its simplest representation: hotspot ( $G_h \times G_p$ ) or coldspot where the species co-occur but  
623 do not coevolve ( $G_p$  or  $G_h$ ); **c.** the outcomes of coevolution are impacted by spatially varying  
624 selection : in a habitat, the strength of the interaction (coldspot or hotspot) between host and  
625 parasite populations can vary depending on within habitat heterogeneity ( $G_h \times G_p$ ,  $G_p$  or  $G_h$ ,  $G_h \times$   
626  $E$  or  $G_h \times E$ ,  $G_p \times G_h \times E$ ), as well as on between habitat heterogeneity ( $G_p \times G_h \times E$ ). Overall, the  
627 heterogeneity in biotic and abiotic interactions among populations and habitats (GxGxE) leads to  
628 a complex pattern of spatially heterogeneous selection. d. Adding demographic processes (*i.e.*,  
629 **effective population size**  $N_e$  and gene flow) to the adaptive processes driven by interactions (*i.e.*,  
630 GxG, GxE and GxGxE) helps to assess variation in selection pressure and the speed of coevolution  
631 over space and time.

632

633 **Figure 2. Practical guide for future studies of coevolutionary dynamics using ecological**  
634 **genomics**