Studying the genetic basis of ecological interactions with intergenomic epistasis

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Abstract

In a community, the phenotype or fitness of genotypes of a focal species can depend on the genotypes of other species. Such between-species genetic interactions are increasingly referred to as intergenomic epistasis, analogous to the classical definition of (intragenomic) epistasis in genetics. Here, we propose the first mathematical definition of intergenomic epistasis, which formalises the minimal conditions for the existence of inter-species genetic interactions. By discussing empirical studies of interacting species from the literature, we argue that intergenomic epistasis is a useful umbrella concept that engulfs multiple co-evolutionary relationships of interacting species, such as genotype-specific or gene-for-gene interactions. Consequently, intergenomic epistasis can be asserted in a study system when (i) the specific ecological interactions are unknown, (ii) the genetic basis of between-species interactions is unidentified, or (iii) the underlying genetic architecture is complex and involves genetic interactions within and between genomes. Moreover, the term itself highlights the importance of genetic factors in the study of ecological interactions, thus encouraging links between research in genetics and ecology. Finally, we argue how models incorporating intergenomic epistasis may facilitate the study of co-evolution.

Keywords: GxG interactions, species interactions, co-evolution, host-pathogen interactions, community genetics, epistasis, eco-evolutionary dynamics, evolutionary theory

Introduction

When species interact, the phenotype or fitness of a focal genotype in one species can depend on the genotypes of other species. The nature of these between-species genetic interactions and their ecological and evolutionary consequences depends on the system they are observed in and on the type of between-species ecological interaction. For example, between-species genetic interactions frequently exist in host-symbiont or host-parasite relationships, where fitness in either species can depend strongly on the genotype of its interacting partner (e.g., Lambrechts et al., 2005; Salvaudon et al., 2005; Webster et al., 2004). In such systems, between-species genetic interactions are associated with **co-evolution** (reviewed in Buckingham and Ashby, 2022; Thompson, 1989; Wade, 2007; see Glossary). In other species, less intuitive between-species genetic interactions play an important role in shaping the local ecological community. One example of this is the mimicry success of a *Heliconius* butterfly, which depends on the colour morphs present in the local butterfly community. In this example, the genetically determined morph composition of a focal species depends not only on the presence of other butterfly species but also on the genotypic diversity within each species that encodes the intraspecific phenotypic variation in colour morphs (Merrill et al., 2015; Sherratt, 2008). Thus, the outcomes of many ecological interactions depend on the segregating genetic variants of multiple species living in a community, linking the reproductive success of an individual not only to its own genotype but also to the genotypes present in the same and other species.

The above examples illustrate how species' genomes interact with each other and how this interaction can affect ecological and evolutionary processes. We here focus on interactions between genotypes because, even though the mapping between genotypes, phenotypes, and fitness is complex (e.g., involving development and plasticity), ultimately, there is an underlying genetic basis of heritable variation (e.g., Promislow, 2005). Known consequences of between-species genetic interactions are their effect on genetic diversity within and across species (Hafer-Hahmann & Vorburger, 2020), their involvement in ecosystem processes (reviewed in Stange et al., 2020; Whitham et al., 2012), and their impact on evolutionary trajectories of species (Kauffman & Johnsen, 1991). Due to their ecological and evolutionary importance, there is great interest in describing between-species genetic interactions meaningfully. Recently, such between-species genetic interactions have increasingly been referred to as **intergenomic epistasis**,

analogous to the classical definition of **(intragenomic) epistasis** in genetics (Batstone, 2022; Heath, 2010; Sørensen et al., 2021; Turkarslan et al., 2021; Wade, 2007).

Here, we discuss the concept of intergenomic epistasis as a means of studying the genetic basis of ecological interactions. Guided by a mathematical definition of intergenomic epistasis (Box 1), (i) we lay out how intergenomic epistasis is a useful umbrella term that encompasses central concepts commonly used to describe between-species genetic interactions, (ii) we explain how studying intergenomic epistasis can improve our understanding of the genetic architecture of traits underlying ecological interactions, and (iii) we argue how, as a natural extension of intragenomic epistasis, intergenomic epistasis provides a genetics-aware avenue of deciphering co-evolution between species.

Intergenomic epistasis as an umbrella term for between-species genetic interactions

The concept of intergenomic epistasis was first synthesised by Wade (2007), focussing on the selective pressures that favour co-transmission of gene combinations across species in the context of **community genetics** (Antonovics, 1992) (*cf.* the **extended phenotype** by Dawkins (1982), or **Indirect Genetic Effects** (IGEs) by Wolf et al. (1998)). Since Wade (2007), various notable empirical studies investigating intergenomic epistasis have been published (Gupta et al., 2022; Heath, 2010; Sørensen et al., 2021; Turkarslan et al., 2021). For example, Heath (2010), Sørensen et al. (2021), and Turkarslan et al. (2021) studied intergenomic epistasis in mutualistic systems, in which different between-species genotype combinations affected fitness of interacting species. Such genetic interactions have previously been described as **genotype-specific** or genotype-by-genotype ($G \times G$) interactions. In this Section, we present (i) other commonly used concepts describing between-species genetic interactions, such as genotype-specific interactions and allele-matching, (ii) a mathematical definition of intergenomic epistasis, and (iii) how we can differentiate between different genetic mechanisms underlying ecological interactions, in order to establish the standing of intergenomic epistasis as an umbrella term.

Known mechanisms underlying between-species genetic interactions

There is a rich literature on the topic of between-species genetic interactions, especially in the context of host-pathogen systems. A common way of differentiating between genetic interaction types is by classifying them based on their varying degrees of specificity, i.e. whether interactions are mediated at the

genotype- or individual-gene level (e.g., reviewed in Buckingham and Ashby, 2022). For example, when interactions between different pairs of genotypes produce distinct phenotypes, they are often described as genotype-specific (comprehensively illustrated in Box 2 of Lambrechts et al. (2006)). Genotype-specific interactions have been observed in systems with mutualistic (Heath, 2010; Heath & Tiffin, 2007; M. P. Parker, 1995; Sørensen et al., 2021; Turkarslan et al., 2021), host-parasite (Carius et al., 2001; Lambrechts et al., 2005; Peever et al., 2000; Salvaudon et al., 2005; Webster et al., 2004) and defensive symbiotic interactions (Hafer-Hahmann & Vorburger, 2020; B. J. Parker et al., 2017). In host-pathogen systems, it was suggested that genotype-specific interactions are associated with **negative frequency-dependent selection**. Here, pathogens evolve to infect abundant host genotypes, and hosts evolve to be resistant against abundant pathogen genotypes, which can lead to co-evolutionary arms races with **Red Queen dynamics** driven by reciprocal selection acting on coupled genes (reviewed in Brockhurst et al., 2014; Christie and McNickle, 2023; Ebert and Fields, 2020).

Genotype-specific interactions are often described in systems using lines or strains that were isolated from nature (e.g., Salvaudon et al., 2005) where the exact genetic basis of the traits mediating the ecological interaction may be unknown. However, in some well-studied host-parasite systems, pathogenicity could be attributed to the state of individual genes. Such gene-specific interactions, often termed **gene-for-gene interactions**, have been described in several plant-pathogen systems (reviewed in Flor, 1956; Thompson and Burdon, 1992). Even more specific **allele-matching** systems were discovered in host-parasite systems such as in *Daphnia magna* and the parasitic bacterium *Pasteuria ramosa* (Bento et al., 2017; Luijckx et al., 2013). Gene-for-gene interactions and allele-matching are usually considered qualitative resistance mechanisms that rely on the recognition, or the "matching", of complementary genes or alleles in host and pathogen (Thrall et al., 2016). For example, classical gene-for-gene interactions in plant-pathogen systems work via pattern-recognition-receptors in the plant that bind pathogen virulence factors. Binding of the virulence factors and thus recognition by the plant triggers the plant's immune system, leading to resistance. Direct mapping of such plant receptors to their corresponding resistance genes and pathogen virulence factors to their respective **avirulence genes** has been successful in cultivated flax (e.g., Flor, 1956), wheat (e.g., Hatchett and Gallun, 1970), rice (e.g., Jia et al., 2000), and various other crop systems (e.g, Chen et al., 2024; Delourme et al., 2007; Van den Ackerveken et al., 1992).

The terms explained above describe how a phenotype or fitness can be affected by genetic variants of a focal species that interact with genetic variants in another species, i.e., they all represent cases of intergenomic epistasis. However, the use and applicability of these terms differ depending on both the research field and the current knowledge of the genetic basis. For example, reports of gene-for-gene interactions are overrepresented in crop systems, which might not necessarily reflect the absence of gene-for-gene interactions from other systems (Ebert & Fields, 2020) but rather be the consequence of historical discoveries in crop systems (e.g., Dodds, 2023; Flor, 1956; Kaur et al., 2021). Furthermore, the classification depends on how well resolved the genetic basis of the trait in question is. For example, before the specific alleles involved in the interaction were discovered, the allele-matching interaction between *D. magna* and *P. ramosa* was described as genotype-specific (Carius et al., 2001; Luijckx et al., 2011). Finally, some systems may not fit the specific categories of genetic interactions laid out above, for example, when resistance and susceptibiliy in a gene-for-gene interaction are not perfectly binary. In the following two sections, we argue how we can resolve some of these challenges by asserting intergenomic epistasis based upon a formal mathematical definition (Box 1).

Intergenomic epistasis covers all between-species genetic mechanisms

Epistasis traditionally describes genetic interactions within the same genome of an individual (Box 2). However, the concept of epistasis naturally extends to describing genetic interactions between species, also referred to as intergenomic epistasis (Wade, 2007) (see Box 3 for different applications of the terminology). In the context of ecological communities, intergenomic epistasis is used to describe genetic interdependence between ecologically interacting species (Batstone, 2022; Heath, 2010; Sørensen et al., 2021; Turkarslan et al., 2021, and reviewed in Wade, 2007). Accordingly, already Flor, the first to describe gene-for-gene interactions in cultivated flax *Linum usitatissimum* and its fungal pathogen, flax rust *Melampsora lini* (Flor, 1942), highlighted that "[...] the genetics of rust resistance involves the study of the interaction of the genes conditioning reaction in the host with those conditioning pathogenicity in the parasite" (Flor, 1956).

The original verbal definition of intergenomic epistasis is based on the statistical definition of epistasis (Wade, 2007) *sensu* Fisher (1919), commonly used in population genetics (Lehner, 2011; Phillips, 2008; see Box 2). This statistical definition describes epistasis as genetic interactions between loci that lead to

non-additive effects on a phenotype or fitness. Noting down the mathematics of this statistical definition (see Box 1) shows that intergenomic epistasis captures the overarching phenomenon of all between-species genetic interactions, which can be broken down into varying levels of specificity depending on the genetic details that confer non-additive fitness effects (see Fig. 3). Consequently, concepts such as gene-for-gene interactions and allele-matching emerge as subcategories of intergenomic epistasis, for which the genetic interactions between the interacting species result from specific genetic mechanisms.

Non-zero interaction terms indicate the genetic mechanisms underlying intergenomic epistasis

We propose a mathematical model to (i) formally define intergenomic epistasis, (ii) describe between-species genetic interactions, and (iii) differentiate between different genetic mechanisms that underlie ecological interactions (Box 1). Following our understanding of intergenomic epistasis explained above, we define intergenomic epistasis in the mathematical model as any between-species interaction where the measured phenotype or fitness of a genotype in a focal species is affected by the genome of at least one partner species. Therefore, intergenomic epistasis in our model can arise due to effects of single genetic variants in a partner species' genome, by genetic interactions involving pairwise or higher-order epistatic effects, or a combination of both (see Fig. 2 for examples).

The mathematical definition delineates the conditions to assert different genetic mechanisms compatible with the flowchart in Fig. 3. Inference of the interaction parameters (as exemplified in Figure Fig. 2) categorises genetic interaction types and demonstrates how they all fit under the umbrella of intergenomic epistasis. For example, we find that pairwise or higher-order effects can play an important role in much-studied genetic interactions such as gene-for-gene interactions and allele-matching (Fig 2c,d). Here, the epistatic interactions across genomes are not only essential for the mechanism of resistance (here, the "matching" of genes or alleles) but are also masking the presence of multiple resistance genes. This masking is a specific feature of qualitative resistance mechanisms (Thrall et al., 2016).

Notably, according to our definition, the assertion of intergenomic epistasis is specific to the focal species. This implies that intergenomic epistasis includes effects on phenotype or fitness of a focal species caused by genetic variants in the partner species without requiring reciprocal effects on the partner species. In this case, the observed effects are comparable to genotype-by-environment ($G \times E$) interactions.

Investigating the genetic basis of between-species ecological interactions with intergenomic epistasis

In the previous section, we highlighted different genetic mechanisms of between-species interactions and how they fit under the umbrella concept of intergenomic epistasis. In this section, we propose how to apply this knowledge to assess genetic interactions in natural systems. To this end, we discuss (i) how to assert intergenomic epistasis in a system of ecologically interacting species and (ii) how identifying intergenomic epistasis helps investigate interactions with a complex genetic basis.

How to assert between-species genetic interactions

With the continued development of genomic tools, new methods for detecting between-species genetic interactions are emerging. Various reviews have discussed options for how to detect genomic signatures of genetic interdependence (e.g., see Ebert and Fields, 2020; Märkle et al., 2021; Nuismer et al., 2022). Newly developed approaches allow for the joint analysis of polymorphism data of interacting species. One example of such joint genome analysis is to perform co-evolutionary Genome Wide Association Studies (co-GWAS) between interacting species (reviewed in Märkle et al., 2021; Nuismer et al., 2022). Co-GWAS reveal associations between polymorphisms in interacting species, which can be quantified as interspecies linkage disequilibrium (iLD) (reviewed in Ebert and Fields, 2020). In particular, Märkle et al. (2024) recently developed a co-GWAS approach to infer different patterns of genotype-specific interactions in human-pathogen systems. The authors categorised interactions based on a given set of interaction patterns (such as gene-for-gene interactions or allele-matching interactions). Using this method, they inferred gene-for-gene interactions between variants at the human major histocompatibility complex (MHC) and Hepatitis C virus.

In a complementary manner, our mathematical definition asserts to which extent within-species genetic variation that is associated with genetic variation in a (putatively) interacting species (e.g. identified using co-GWAS) satisfies the definition of intergenomic epistasis. To apply our model to empirical data, we would ideally measure a focal phenotype or fitness metric in multiple between-species (isogenic) genotype combinations. This would allow us to fit the proposed system of equations and to infer the interaction terms within and between genomes (see Fig. 2 for examples). In the minimal case, inferring

intergenomic epistasis for a focal species requires comparing measurements of a phenotype of interest when the same genotype of the focal species is grown in the presence of each of two genotypes of one partner species. Inferring reciprocal intergenomic epistasis or genotype-specific interactions as described by the 2-species 2-locus model presented in Box 1 would require phenotype (or fitness) measurements for all four genotype combinations of focal and partner genotypes; the model and test requirements become more complex if multiple loci or species are to be considered.

A strength of our proposed approach is that the assessment of between-species genetic interactions does not require *a priori* knowledge or assumption of the specific interaction type between the species. Moreover, no detailed understanding of the genetic basis underlying the interactions is necessary; the model can be applied at the strain, locus or allele level and the inference can be readjusted or refined when additional genetic information becomes available. Denoting the interaction type as gene-for-gene interactions *versus allele-matching, for example, can be done* a posteriori when the necessary resolution of the genetic data is available.

Frequency-dependent selection could pose challenges to the inference of interaction parameters when multiple genotypes are segregating in a population. These challenges are circumvented when individual genotypes or strains of the interacting species are available to allow for the experimental assessment of reciprocal between-species genotype combinations. However, measuring the focal phenotype across combinations of populations with differently abundant genotypes in nature could yield approximate estimates of the model parameters when such experiments are impossible.

The mathematical definition of intergenomic epistasis captures complex genetic architectures

Asserting the mere presence of intergenomic epistasis between ecologically interacting species is a first step to understanding genetic interdependence between species. The second step is to identify the genetic interaction type. This identification can be complicated when there are complex genetic interactions between multiple genes within and across genomes (Langlands-Perry et al., 2023; Sugihara et al., 2023). For instance, Langlands-Perry et al. (2023) described the complex genetic interactions underlying the infection of wheat (*Triticum aestivum*) by the fungal pathogen *Zymoseptoria tritici*. In this system, fungal pathogenicity is polygenic and depends on individual gene-for-gene interactions, as well as on the fungal genetic background, due to intragenomic epistasis within the fungal genome (Langlands-Perry

et al., 2023). Describing this interaction as strictly gene-for-gene would be reductive and missing out on the importance of the intragenomic epistasis that shapes the outcome of fungal infection. Besides showing the involvement of complex genetic interactions, this example highlights how the classification of genetic mechanisms depends on the genetic information available. For example, testing resistance of wheat to different pathogenicity genes of *Zymoseptoria tritici* on the same fungal background would reveal gene-for-gene interactions but be insufficient to detect the effects of intragenomic epistasis in the fungal genome.

If we applied our mathematical definition (extended to multiple loci) to the above explained wheat-*Z. tritici* system, we would likely classify the interaction between the two species as genotype-specific rather than a gene-for-gene interaction since the resistance mechanism is not strictly qualitative. Moreover, we could use our model to infer the complex interactions in detail, e.g. by including intragenomic epistatic terms (see Fig. 1b). Here, conceptualising between-species genetic interactions through the lens of intergenomic epistasis challenges us to dissect the specific kinds of interactions between genomes and the resulting genetic architecture. Thus, our proposed approach adds a genetics-aware route to studying ecological interactions.

Deciphering co-evolution through intergenomic epistasis

So far, we have explained how using epistasis to address the genetic interdependence between species puts emphasis on the genetic architecture of the traits involved in ecological interactions. In this section, we address the role of intergenomic epistasis in the study of co-evolution. Following our definition of intergenomic epistasis, where genetic change in one species can affect phenotypes or fitness in another species, we infer that intergenomic epistasis (i) is a prerequisite for co-evolution, and (ii) captures the genetic interactions underlying co-evolution (Carmona et al., 2015). From this, two important propositions arise, namely that (i) asserting intergenomic epistasis could identify the early stages of co-evolution, and that (ii) we can borrow concepts from research on (intragenomic) epistasis to study co-evolution.

Intergenomic epistasis as a prerequisite for co-evolution

Our definition of intergenomic epistasis in Box 1 is species-specific; an interaction between species that is considered intergenomic epistasis for one species in a species pair might not satisfy the definition of intergenomic epistasis for the other species. This could be the case in species pairs for which the strength of the ecological interaction between species is asymmetric. We can imagine such asymmetrical interactions in systems where interactions are newly established; a hypothetical example is given below. In such cases, the identification of intergenomic epistasis could mark co-evolution in its early stages. In contrast, ongoing co-evolution would be characterised by reciprocal intergenomic epistasis (e.g., genotype-specific interactions).

For example, in cross-feeding interactions (reviewed in Smith et al., 2019), one species might evolve a genotype with increased metabolite secretion, which increases the fitness of the partner species feeding on it. Here, fitness in the partner species will depend on the presence of the secretion variant, leaving a statistical signal of intergenomic epistasis. At this stage, there might not be any fitness increase for the species that secretes the metabolite. The initially one-sided relationship can lead to interspecies cooperation (e.g., Douglas et al., 2017) and, eventually, co-evolution, when it results in reciprocal adaptations between species. By determining how the genetic background of two interacting species affects cross-feeding, we can determine potential drivers of ecological interactions and predict incipient co-evolution. Identifying the genes that mediate interactions, such as cross-feeding relationships, is important for understanding the cooperation and evolution of ecological systems like the gut microbiome (Culp & Goodman, 2023; Rakoff-Nahoum et al., 2016). Furthermore, by asserting intergenomic epistasis, we can point out genetic dependencies that have potential ecological and (co-)evolutionary consequences but that do not fit strict co-evolutionary concepts of genetic interactions contingent on reciprocity.

Revealing new co-evolutionary dynamics through intergenomic epistasis

In addition to using inferred intergenomic epistasis as a putative indicator of co-evolution, we propose that considering theoretical models of intergenomic epistasis can advance the study of co-evolutionary dynamics. Specifically, borrowing concepts established in the context of intragenomic epistasis allows researchers to investigate co-evolution in communities through the lens of intergenomic epistasis. For

example, intragenomic epistasis is known to constrain evolutionary trajectories (reviewed in Bank, 2022; Fragata et al., 2019; Johnson et al., 2023), e.g. by altering adaptive routes favoured by selection (McLeod & Gandon, 2022), or by introducing historical contingencies, where mutations are only beneficial when they appear in a specific genetic background (Blount et al., 2012, 2008; Karageorgi et al., 2019; Nosil et al., 2020). Applying the framework of epistasis to ecological systems carries the potential to reveal similar mechanisms in pairs of interacting species, providing new insights into co-evolutionary processes.

In this vain, Gupta et al. (2022) experimentally studied the co-evolution between the bacteriophage λ and its host *Escherichia coli*, showing cross-species historical contingencies. Specifically, the phage was more likely to evolve a second path for invasion of *E. coli*, if adaptation to resistant *E. coli* was preceded by a phase of adaptation to ancestral *E. coli*. This led the authors to update a previous model of co-evolution between the two species (Meyer et al., 2012). Moreover, the authors found host-dependent epistasis (mutation-by-mutation-by-host interactions), which might affect the course of the phage's evolution by impacting the phage's range of infectivity (Ashby et al., 2014). This study is a powerful example of how explicitly considering intergenomic epistasis improves our understanding of co-evolution.

Conclusions

Genetic interactions among and between species have important consequences on fitness and evolution of species, as evidenced by an increasing body of literature from different fields. Multiple established concepts describe different mechanisms of genetic interactions between species at varying levels of specificity. Here, we argued by means of a mathematical definition how intergenomic epistasis can be used as a flexible umbrella term encompassing such between-species genetic interactions. Our formalised definition of intergenomic epistasis characterises the genetic architecture underlying between-species interactions. We propose this definition as universal reference for researchers who investigate between-species genetic interactions. Our definition flexibly incorporates genetic mechanisms of varying levels of specificity and complexity, thus encouraging a closer look at the genetic architecture underlying ecological interactions.

Beyond using intergenomic epistasis as a descriptor for genetic dependence between species, we highlighted potential applications of intergenomic epistasis for the study of co-evolution. Namely, we proposed intergenomic epistasis as a prerequisite for co-evolution and as a driver of ongoing co-evolution. Thus, the concept of intergenomic epistasis provides a framework for studying co-evolution in ecological

systems. Approaching systems of interacting species through the lens of intergenomic epistasis opens up new ways of investigating systems of genetic (inter)dependence by borrowing tools from studying intragenomic epistasis. Borrowing from research on epistasis is a natural step to advancing the field of co-evolution because much of the study of co-evolution is already centred around interactions between genes of interacting species. In this context, we encourage researchers to consider interacting species with respect to intergenomic epistasis because its detection paves the way to explaining (co-)evolutionary dynamics (e.g., Gupta et al., 2022; Kauffman and Johnsen, 1991) and advancing our understanding of co-evolution.

Concludingly, we see intergenomic epistasis as a promising concept that bridges genetics, ecology and evolution, which carries great potential for the study of eco-evolutionary dynamics.

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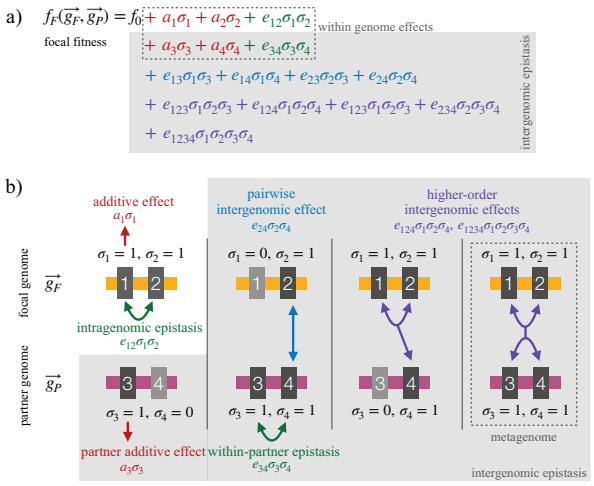

Figure 1: Visual representation of our mathematical definition of intergenomic epistasis in Box 1, where fitness of a focal species $f_F(\vec{g_F}, \vec{g_P})$ depends on its own genotype $\vec{g_F}$ and the genotype of a partner species $\vec{g_P}$ in a two-species community ($\vec{S} = \{F, P\}$). **a)** shows the full mathematical definition with all possible interaction terms between loci within and between genomes for two loci in both genomes of the species pair ($L_F = L_P = 2$), i.e. a total of four loci ($i = 1, 2, 3, 4$). All terms that represent the effect of $\vec{g_P}$ on $f_F(\vec{g_F}, \vec{g_P})$ and therefore contribute to intergenomic epistasis are highlighted with a grey box. We further highlight terms that contribute to $f_F(\vec{g_F}, \vec{g_P})$, which do not involve any direct interactions between the two genomes ("within-genome effects"). Where the two boxes intersect, we find terms that contribute to the fitness of the focal species, f_F, independently of the focal genome. According to our definition, these terms, when non-zero, indicate intergenomic epistasis; however, one could alternatively (or additionally) classify these terms as indicators of genotype-by-environment interactions ($G \times E$), where the focal species's fitness is altered by the biotic environment (which, here, is given by the partner genotype). **b)** is a visual representation of the types of interactions between loci that are encoded in a). Each panel represents a metagenome containing loci $i = 1, 2$ that are located in the focal genome (orange), and loci $i = 3, 4$ that are located in the partner genome (purple). Each locus i can carry a genetic variant ($\sigma_i = 1$, dark grey) which can cause deviations from f_0 ($\sigma_i = 0$, light grey). Again, we highlight interactions contributing to intergenomic epistasis with a grey box. From the left: in the first panel, in the focal genome we indicate genetic effects on fitness f_F that do not fall under the intergenomic epistasis umbrella, such as additive effects at loci in the focal genome g_F (e.g., $a_1\sigma_1$, red arrow), or epistatic interactions between loci in the focal genome g_F (e.g., $e_{12}\sigma_1\sigma_2$, green arrow), and in the partner genome we indicate how genetic variants at individual loci can introduce intergenomic epistasis (e.g., $a_3\sigma_3$, red arrow); in the second panel we show interactions between two loci that can cause intergenomic epistasis, if at least one (e.g., $e_{24}\sigma_2\sigma_4$, blue arrow) or both of them (e.g., $e_{34}\sigma_3\sigma_4$, green arrow) are located in the partner genome. Finally, we depict higher-order intergenomic interactions between three or more loci across genomes (e.g., $e_{124}\sigma_1\sigma_2\sigma_4, e_{1234}\sigma_1\sigma_2\sigma_3\sigma_4$, purple arrows).

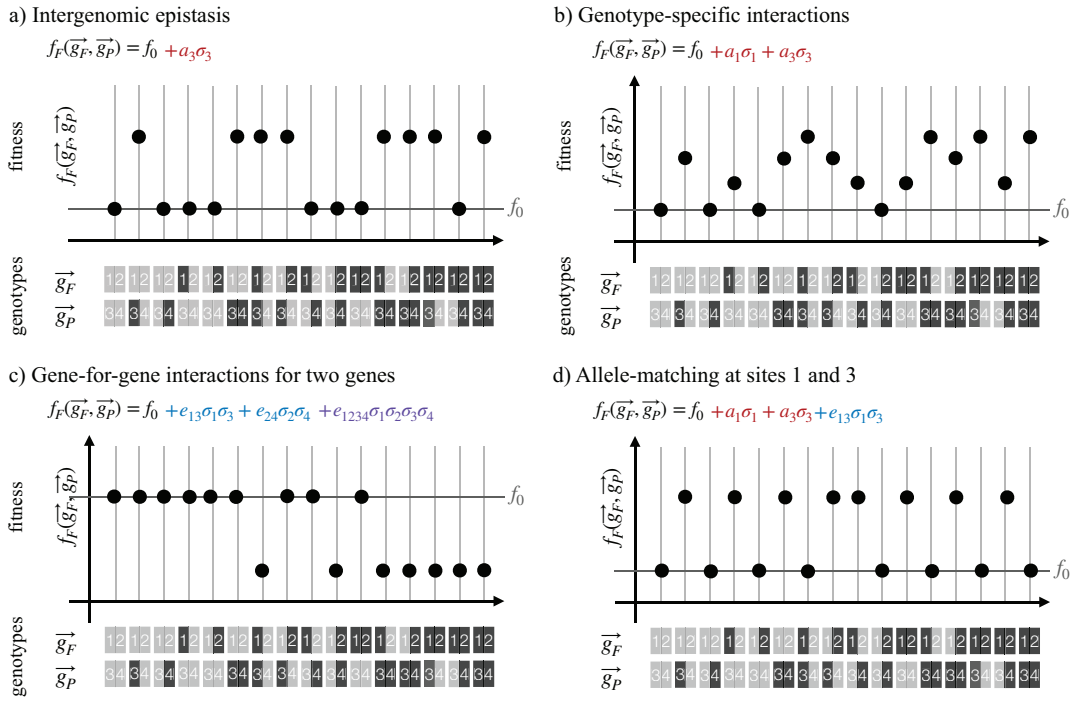

Figure 2: Illustration of potential fitness patterns when there is intergenomic epistasis. Here, we show examples of how the fitness of a focal species $f_F(\vec{g_F}, \vec{g_P})$ could depend on the focal genotype ($\vec{g_F}$; different genetic variants in light and dark grey) and its interactions with the genotype of a partner species ($\vec{g_P}$; different genetic variants in light and dark grey), how these patterns are captured by our mathematical definition, and how we would categorise the interaction type according to the flowchart in Fig. 3. As in Fig. 1 we show four loci ($L = 2$ for two species), where loci $i = 1, 2$ are located in the focal genome and loci $i = 3, 4$ are located in the partner genome. In **a)**, the focal species has increased fitness when the partner species carries a genetic variant at locus three ($\sigma_3 = 1$), which qualifies as intergenomic epistasis. However, the genotype of the focal species, $\vec{g_F}$, does not have an effect on focal or partner fitness, which is why we would not consider this a genotype-specific interaction. Indeed, this is arguably a genotype-by-environment interaction, where the ($\sigma_3 = 1$) effectively changes the biotic environment for the focal species. In **b)**, the fitness of the focal species depends on the combination of focal and partner genotypes. Since the focal species' fitness $f_F(g_F, g_P)$ depends on both g_F and the genotype it is paired with g_P, interactions are genotype-specific. Here, this interaction is mediated by one locus in each species ($i = 1, 3$). In **c)** and **d)**, the genotype-specificity is mediated by individual genes, either by species matching genes (gene-for-gene interactions **c)**), or alleles (allele-matching **d)**), resulting in qualitative ("all-or-nothing") resistance patterns.

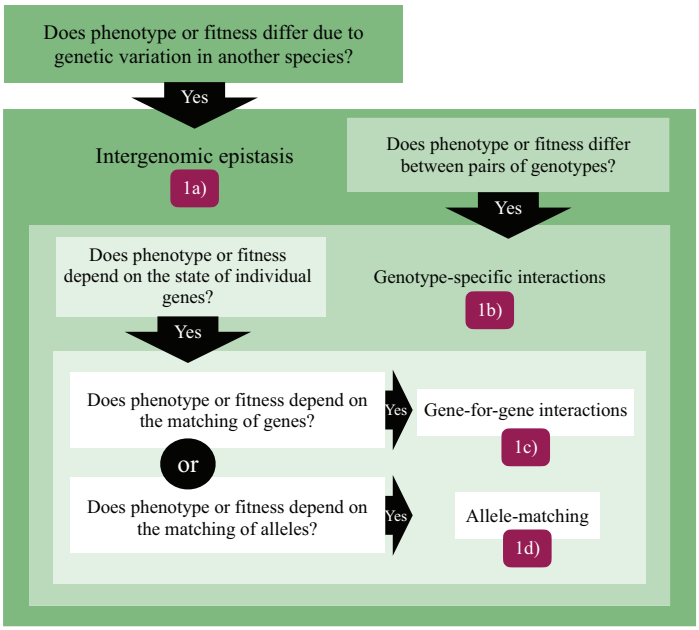

Figure 3: We propose intergenomic epistasis as a useful umbrella term for between-species genetic interactions that encompass different genetic mechanisms. Here, we subdivide types of genetic interactions according to their known specificity. We move from a general understanding of genetic interdependence between species to concrete and highly specific genetic interactions at the gene or allele level. We propose a mathematical definition elaborated in Box 1 to classify the types of genetic interactions according to this flowchart. Empirical application of this definition would require measuring a phenotype of interest or fitness across genotype combinations, followed by inference of additive and interaction terms. Purple boxes correspond to the panels in Fig. 2 that represent exemplary patterns of fitness expected for different interaction types.

Box 1: Formal mathematical definition of intergenomic epistasis

We define a mathematical model to describe the minimal conditions for intergenomic epistasis and to distinguish between different mechanisms of between-species genetic interactions. In the most general definition, consider a community of N species, $\vec{S} = \{S_1, S_2, \ldots, S_N\}$. Each species S_k is represented by a genome of length L_{S_k}, where each genotype $g_{\vec{S_k}}$ is a vector of L_{S_k} loci with m possible genetic variants from the set $A = \{\alpha_1, \alpha_2, \ldots, \alpha_m\}$. For example, genetic variants could be considered binary ($m = 2$), encompass nucleotide variants ($m = 4$), amino-acid variants (m=20), structural or antigen variants (m as (large) integer, potentially depending on S_k), depending on the available data, study system, and research question. We express the fitness of a focal species S_k as a function of the genotypes of all species in the community, $f_{S_k}(g_{\vec{S_1}}, ..., g_{\vec{S_{N-1}}})$, which is determined by additive effects at each locus and interaction effects between loci within and between species. (Common empirical fitness measures or proxies of fitness are growth rate, lifetime reproductive success, or survival. Alternatively, we could measure a phenotype of interest, such as above-soil biomass of plants in a meadow community.) In the following, we describe the conditions for intergenomic epistasis in a two-species community with two loci and two genetic variants per locus per species.

Consider two species $\vec{S} = \{F, P\}$, representing a "Focal" and a "Partner" species, with $L_{tot} = L_F + L_P$ diallelic loci, where each locus i in the resulting **metagenome** is encoded by $\sigma_i \in \{0, 1\}$ to represent the absence (0) or presence (1) of a genetic variant. Loci $i \leq L_F$ correspond to loci in the genome of the focal species F, and loci $L_F < i \leq L_{tot}$ correspond to loci in the genome of the partner species P. We then compute the fitness of the focal species $f_F(g_{\vec{F}}, g_{\vec{P}})$ as a function of the genotype of the focal species $g_{\vec{F}}$ and the genotype of the partner species $g_{\vec{P}}$. $f_F(g_{\vec{F}}, g_{\vec{P}})$ is defined by a baseline ("wildtype") fitness f_0 plus additive effects a_i of genetic variants at each locus i, pairwise epistatic terms e_{ij} between two loci i and j, for $i \neq j$, and higher-order epistatic terms $e_{ij...}$, for genetic interactions within and between genomes (see Fig. 1b). We present the resulting equations for $\vec{S} = \{F, P\}, L_F = L_P = 2$ in Fig. 1a. (The notation can be adapted to multiplicative effects when desired, e.g., in the context of discrete-time theoretical models.)

In the two-species community $\vec{S} = \{F, P\}$, we define the minimal conditions for (i) intergenomic epistasis and (ii) genotype-specific interactions, and the criteria for (iii) gene-for-gene interactions and

(iv) allele-matching. (i) The minimal condition for intergenomic epistasis in our model is met when the focal fitness $f_F(\vec{g_F}, \vec{g_P})$ depends on at least one interaction term that involves a locus in the partner genome ($i > L_F$; see grey box in Fig. 1). This includes all pairwise or higher-order interactions between genomes, additive effects at loci in the partner genome (a_i for $i > L_F$), and genetic interactions within the partner genome (e.g., e_{ij} for $i, j > L_F$; "within partner epistasis"). Thus, according to our definition, intergenomic epistasis can be caused by a single (additive) genetic variant in the partner genome and does not require reciprocal genetic interactions between genomes (see Fig. 2a). Essentially, such additive effects at loci in the partner genome (a_i for $i > L_F$) correspond to genotype-by-environment interactions, where the environment is represented by the genotype(s) of the partner species. Notably, the assessment of intergenomic epistasis in our model is specific to the focal species.

Following the flowchart in Fig. 3, the minimal conditions for genotype-specific interactions are satisfied when the focal fitness $f_F(\vec{g_F}, \vec{g_P})$ depends on at least one interaction term that involves a locus in the partner genome and at least one locus in the focal genome. This can mean two separate interaction terms (e.g., a_i and a_j for $i \leq L_F, j > L_F$; see Fig. 2b), or a single interaction term describing pairwise or higher-order epistatic interactions between loci in both genomes (e.g., e_{ij} for $i \leq L_F, j > L_F$). Gene-for-gene interactions require pairwise epistatic interactions between loci in both species (the "matching" mechanism) and higher-order epistatic effects masking the effects of multiple resistance genes due to the qualitative nature of gene-for-gene resistance mechanisms (Thrall et al., 2016) (see Fig. 2c). Finally, allele-matching requires additive effects in the focal and the partner species for alleles conferring resistance, and pairwise epistatic interactions between the loci of both genomes to "match" the alleles (see Fig. 2d).

Box 2: The definition(s) of epistasis

Originally, epistasis was described by Bateson (1909) as the suppression of an allelic phenotype by an allele at another locus. However, epistasis has a long history of being used to describe various phenomena (e.g., reviewed in Domingo et al., 2019; Lehner, 2011; Phillips, 2008). Some of these definitions of epistasis are focused on molecular interactions of gene products (e.g., functional epistasis (Phillips, 2008), whereas other definitions are statistical in nature (e.g., in the context of fitness landscapes (e.g., Fragata et al., 2019) or population genetics (Lehner, 2011; Phillips, 2008)). Here, we use epistasis in its statistical

sense to describe interactions between genetic variants that lead to non-additive effects on a phenotype or fitness. This statistical definition, originally proposed by Fisher (1919), measures epistasis as the deviation from the additive combination of two genetic variants in their effect on a phenotype or fitness.

Although intergenomic epistasis is conceptualised here as a statistical relationship, mechanistic definitions of epistasis, such as the above-mentioned functional epistasis, can be satisfied as well. For example, in a system in which the interaction between a pathogen and its host is mediated by pattern-recognition-receptors (e.g., in gene-for-gene interactions), changes in the receptor's binding affinity affect the outcome of the pathogen's host invasion, essentially displaying functional intergenomic epistasis (see Dodds and Rathjen, 2010; Kaur et al., 2021; Märkle et al., 2022 for reviews on the molecular basis of plant-pathogen interactions). Defining intergenomic epistasis primarily as a statistical relationship rather than a mechanistic one encompasses the effects of many types of genetic interactions mediated by single proteins or more complex phenotypes.

Box 3: Applications of intergenomic epistasis

Usually, epistasis refers to interactions between genetic variants in the same genome. However, the term intergenomic epistasis was coined to describe interactions between genetic variants in different genomes. This concept has been applied to study genomic interactions at different levels, from within to between individuals, and between individuals of the same or different species. Intergenomic epistasis within an individual has been used to describe interactions between mitochondrial and nuclear DNA (e.g., Dowling et al., 2007; Immonen et al., 2020) and hybrid incompatibilities (e.g., Woods et al., 2009). Intergenomic epistasis between individuals has been described in socially interacting individuals of the same species, such as ants, where the interactions between genotypes can affect brood development (e.g., Linksvayer, 2007; Piekarski et al., 2023; Teseo et al., 2014), or in ecologically interacting individuals of different species, as discussed in this paper.

Glossary

Allele-matching	an interaction type where, if a parasite's alleles match the alleles of its host, infection is successful. This is a qualitative resistance mechanism that either results in complete resistance or full susceptibility based on the pairing of genetic variants between focal and partner species.
Avirulence genes	genes in pathogens that encode proteins which bind to receptors in the host, encoded by corresponding resistance genes, which allow the host to recognise the infection and defend itself against the pathogen.
Co-evolution	selective pressures in two species leading to reciprocal evolutionary changes.
Community genetics	a research field concerned with the genetic processes between and among co-evolving species in an ecological community.
Extended phenotype	the phenotypic effects of genes outside of the individual they are expressed in, i.e. effects on the environment, other individuals of the same species, or individuals from other species.
Gene-for-gene interactions	an interaction type where, if a resistance gene in the host matches a corresponding avirulence gene in the pathogen, the pathogen is recognised by the host and infection is unsuccessful.
Genotype-specific interactions	an interaction type where different pairs of interacting genotypes produce different phenotypes or fitness. This interaction type is sometimes also referred to as genotype-by-genotype interactions.
Indirect Genetic Effects	the effects on a phenotype in a focal individual caused by genes that are expressed in another individual; usually applied to interactions between individuals of the same species.
Intergenomic epistasis	genetic interactions between genes in different genomes; here we use intergenomic epistasis in the context of genetic interactions between ecologically interacting species - for other applications of the term, see Box 3.

Intragenomic epistasis	genetic interactions between genes in the same genome and individual; this is the classic application of the term epistasis (see Box 2 for definitions of epistasis).
Metagenome	in our mathematical model, we treat the genomes of all interacting species in a community as a single genome (thus a metagenome) to facilitate the description of the genetic interactions between genetic variants of different species.
Negative frequency-dependent selection	when genotypes at low frequencies are at a selective advantage, and genotypes at high frequencies are at a selective disadvantage.
Red Queen Dynamics	evolutionary dynamics in a species pair, where each adaptation in the focal species is matched by a counteracting adaptation in the partner species, resulting in continual evolutionary change, where the average relative fitnesses of the interacting species remain approximately constant.

Table 1