Epistasis

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Abstract

Epistasis is broadly synonymous with gene interaction, referring to cases in which the effects of changing a gene depend on the state of other genes. Beyond this, the term has acquired a number of different technical and nontechnical meanings, which has led to confusion and misunderstanding in communication across disciplines. Clear communication about epistasis is particularly pertinent in evolutionary developmental biology both because of the relevance of epistasis to some of its key research questions such as the evolution of evolvability and canalization, and because evo-devo acts as a trading zone for cross-disciplinary communication.

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Introduction

In genetics, the term "epistatic" was introduced by Bateson and Punnett to describe deviations from the expected 9:3:3:1 ratio of two independently segregating Mendelian pairs with dominance. In his influential 1909 book on Mendelian inheritance, Bateson used the terms "epistatic" and "hypostatic" to refer to cases in which one factor, the epistatic one, conceals the effects of another, hypostatic, one. Hence, his choice of the Greek term epistatic with the meaning of "upon" "standing" or "stopping." This terminology was in analogy with the contemporary use of the terms dominant and recessive, when one dominant allelomorph (allele) conceals the effects of another recessive one on the same pair (locus). Bateson saw the need for different terms to describe the analogous relationship between alleles at different loci. Bateson did not seem to intend this strictly. Throughout his book he stressed that dominance is not a principle but a matter of degree, and this extends to epistasis. Later, different forms of deviations from the 9:3:3:1 ratio gave name to different types of epistasis such as dominance, recessive, and compositional epistasis.

Bateson's usage was soon supplemented by another concept of gene interaction. In the key 1918 paper unifying Mendelian segregation with the biometric laws of heredity, Fisher noted that the effects of independently segregating factors need not add up in a linear manner, and he coined the term "epistacy" for deviations from statistical additivity. With a century of hindsight it is easy to think that Fisher chose a slightly different term to underline the difference between his statistical and Bateson's biological notion of gene interaction, but Fisher provided no discussion of the matter, and did not make the same terminological distinction with regard to dominance. In any case, Fisher's term epistacy eventually slid out of usage and was replaced with epistasis.

This terminological conflation of statistical and biological epistasis has been an obstacle in cross-disciplinary, even within-disciplinary, communication about gene interaction. While biological measures of gene effects are defined as differences between specific genotypes without regard to their relative occurrence, the statistical measures are defined as average deviations of the genotype effects from population averages over all genotypes in a population. The latter makes statistical gene effects and epistasis dependent on the composition of a population, so that common genotypes, for example, tend to have smaller effects than rare genotypes. Within the field of quantitative genetics the statistical definitions of gene effects proved convenient in terms of describing similarities among relatives and predicting the short-term response to artificial selection, but the statistical description of epistasis as a residual from additive effects averaged out the effects of biological epistasis and led to the notion that epistasis was uncommon, inert, and inconsequential for

selection dynamics at least. This clashed with the intuitions of systems-oriented biologists that (biological) epistasis was ubiquitous and essentially important for organismal function and evolution.

Population genetics used a notion of epistasis that is closer to the biological concept than to the statistical concept of quantitative genetics. In theoretical population genetics, the effects of genotypes on fitness are stipulated in advance and not as statistical averages. This is the basis of most of the standard insights on the effects of epistasis on evolution as in Wright's shifting-balance theory, the Bateson-Dobzhansky-Muller model for the evolution of reproductive isolation, coadapted gene complexes, and the evolution of sex and recombination.

Molecular genetics stuck to Bateson's narrow definition of epistasis as a mutation that masks the effect of another mutation on another gene. This was linked to the idea that an epistatic mutation would be in a gene that acted downstream to an hypostatic mutation and that epistasis therefore could be used as a tool to infer position of genes in genetic pathways.

These different notions of epistasis lived side by side during the development of the modern synthesis but came in closer contact in the 1980s. The emergence of an evolutionary quantitative genetics brought the methods and theory of quantitative genetics into evolutionary biology, and the different notions of epistasis and ideas about its importance came in conflict. Evolutionary developmental biology accentuated this with its focus on how the genotype-phenotype map affects evolution. Epistasis is a property of the genotype-phenotype map and plays a crucial role in key research questions of evodevo such as the evolution of evolvability and canalization. The interest in gene regulation and gene networks in evodevo and systems biology also brought the molecular genetics view of epistasis in contact with the epistasis concepts of evolutionary biology.

## Epistasis as a Property of the Genotype-Phenotype Map

Gene products function in complex biochemical pathways and are thus embedded in networks of molecular interaction. The epistasis concept is not used to describe interactions at this level. Instead it describes interactions between the *phenotypic* effects of genetic *changes*, i.e., allele substitutions including mutations. Epistasis is not a property of the gene but a property of two or more gene *substitutions* that may be epistatic in relation to each other. This makes epistasis an aspect of the genotype-phenotype map. The mapping from genotypes to phenotypes is an abstract description of how phenotypic changes relate to genotypic changes. An additive genotype-phenotype map means that any specific substitution of alleles will have the same phenotypic effect regardless of the state of other genes (i.e., regardless of the position in genotype space), so that the cumulative phenotypic effect of several substitutions equals the sum of their individual phenotypic effects. Every deviation from this pattern may be termed gene interaction and again divided into dominance and epistasis depending on whether the composite changes happen at the same or

different loci, although an interaction between two subsequent changes of the same allele is sometimes called intralocus epistasis.

The strategy of modeling the dynamics of single alleles one-by-one was successful in demonstrating the power of natural selection and in elucidating fundamental principles of microevolution, but it has been less helpful in understanding macroevolution, because the additive summation of effects becomes increasingly unrealistic with larger changes. In a sense, additivity is a constant-evolvability assumption that allows little room for genetic constraints to affect evolution.

Epistasis can be conceptualized as nonlinearities in the genotype-phenotype map (e.g., Rice 1998). As shown in Fig. 1, the same genetic change can have different phenotypic effects depending on position in the genotype-phenotype map. Moving from position A to position B, the convexity of the map leads to an increased phenotypic effect. This is called positive epistasis. Moving from position B to position C, the concavity of the map leads to a decreased phenotypic effect. This is called negative epistasis. Moving into the flat areas of the map, genotypic changes are still possible, but their phenotypic effects vanish. This is called canalization (e.g., Flatt 2005). With the map in Fig. 1, the evolvability is high in the middle region, but moving from position B out towards the edges shows how negative epistasis leads to canalization and reduced evolvability. This constitutes an epistatic constraint on evolution, because it is not possible to change the phenotype beyond the limits of the map.

Real genotype-phenotype maps need not be shaped as in Fig. 1. The degree and sign of curvature and the existence and position of absolute limits to phenotypic
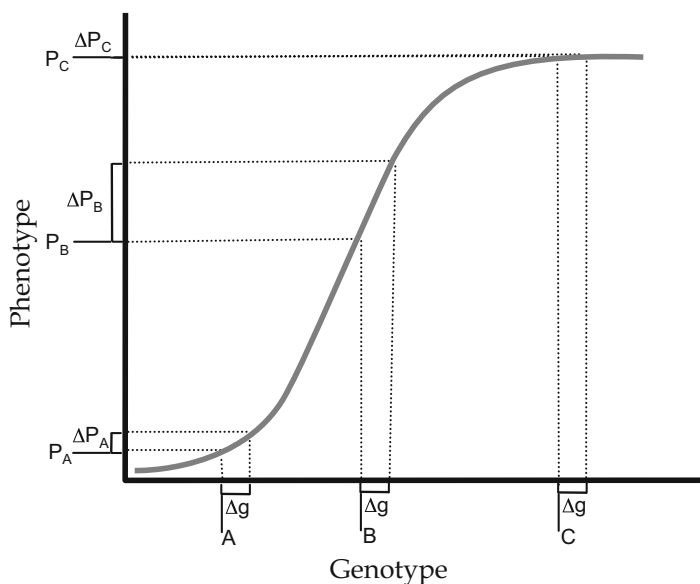
Fig. 1 A nonlinear genotype-phenotype map. The same genetic change, Δg, will have different phenotypic effects, ΔP, depending on the genetic background (positions *A*, *B,* or *C*) in which it happens (Modified from Hansen (2015))

change are empirical questions. The figure illustrates how epistasis allows the evolution of evolvability, and how this depends not on epistasis in general but on particular systematic patterns of epistasis. Positive epistasis in the direction of selection leads to evolution of increased evolvability, while negative epistasis leads to the evolution of decreased evolvability (canalization).

Statistical Epistasis

The Statistical Genotype-Phenotype Map of Quantitative Genetics

The statistical model of the genotype-phenotype map initiated by Fisher is at the core of quantitative genetics. Here genetic effects are defined as statistical deviations from an average. In its modern form the model starts with defining the average effect of an allele as the average deviation of its carriers from the population mean (technically an average excess; the difference between average excess and average effect will be ignored for simplicity). The additive effect (breeding value) of an individual is the sum of these effects for all the alleles it carries. The actual phenotype of the individual may deviate from the breeding value both because of environmental effects and because its genetic component may deviate from the additive sum due to dominance or epistasis. For example, the average deviation of individuals carrying two specific alleles at the same locus may not equal the sum of the average effects of these two alleles. The average deviation from the sum is then the statistical dominance effect of these two alleles. Similarly, the average deviation of individuals carrying two specific alleles at different loci may differ from the sum of the average effects of the alleles, and this difference is a (statistical) epistatic deviation. In general the epistatic effect of any set of alleles is defined as the average deviation of the carriers of this set from the prediction given by taking the sum of all the lower-order effects of these alleles, i.e., the sum of their average effects, dominance effects, and lower-order epistatic effects (Lynch and Walsh 1998).

One may think of the statistical genotype-phenotype map as a multiple regression of individual phenotypes on the presence/absence of alleles and sets of alleles. Dominance and epistasis are interaction effects in this model. The variance explained by the sum of the average effects (i.e., first-order effects) is the additive (A) genetic variance, and the variance explained by the interactions between alleles at the same locus is the dominance (D) variance. There are many different epistatic variances. The variance explained by interactions between two alleles at different loci is the additive-by-additive (AA) epistatic variance, the variance explained by interactions among two alleles at one locus and one at another locus is the additive-by-dominance (AD) epistatic variance, the variance explained by interactions among four alleles at two loci is the dominance-by-dominance (DD) epistatic variance, the variance explained by interactions among three alleles at three different loci is the additive-by-additive-by-additive (AAA) epistatic variance, etc. The sum of all these variances is the total genetic variance.

This decomposition is useful in describing inheritance and similarity between relatives. The covariance between phenotypes of two related individuals is a sum of contributions of all these variance components, each weighted with the probability that the two relatives share the allele sets in question (Lynch and Walsh 1998). For example, full sibs share half the additive effects and thus half the additive variance; they further share one quarter of the dominance effects, one quarter of the AA epistatic effects, and smaller fractions of higher-order epistasis. Offspring and a parent share half the additive variance, none of the dominance variance, one quarter of the AA epistatic variance, and smaller fractions of higher-order AAA types of epistatic variance.

Significantly, because all the alleles carried by an individual are inherited from its two parents, all the additive variance in a generation has been inherited from the previous generation. In contrast, none of the dominance variance and only fractions of the epistatic variances are normally inherited from the previous generation. This is because sets of alleles are broken up and recombined into new combinations each generation.

Epistasis, Inheritance, and Selection

From these considerations, it is clear why the additive effects and the additive variance play central roles in inheritance and selection. Natural selection acts on variation, and the additive variance is the heritable component of the phenotypic variance in a population. Natural selection does not see the difference between components of variance, but only the effects on the additive component are transferred to the next generation and contribute to evolution by natural selection. The smaller fractions of epistatic variance that are inherited, most significantly the one quarter of the AA epistatic variance, can yield a minor evolutionary effect, but this effect is transient because the selected allele combinations are continuously being broken down by recombination. If selection ceases, the gain achieved by selection on epistatic variance is removed at a geometric rate by recombination.

This has served as a theoretical justification for the focus on additive variance in quantitative genetics and for the single-gene perspective of population genetics and most other fields of evolutionary biology. Fisher's average effect is an elegant device for capturing the dynamics of individual alleles without in fact assuming that their effects are biologically additive. In a large population, a specific allele will find itself in myriads of different combinations with other alleles. The effects of selection on the allele will depend on its phenotypic effect averaged over all these combinations, and this is precisely what the average effect is measuring. The definition of statistical epistasis ensures that the epistatic deviations must sum to zero, and hence that they do not affect the dynamics of individual allele frequencies. Hence, the focus on statistical additivity in quantitative genetics is not based on an assumption of biological additivity but on an identification of the statistical averages that govern the dynamics of individual alleles in complex systems of biological interaction.

Statistical and Biological Epistasis

Even though statistical epistasis and epistatic variances are largely inconsequential for evolutionary dynamics, this does not extend to biological epistasis. As the additive effects are averages over genotypes in a population, they will change when the genetic background is changing, and this change is determined by biological epistasis. In Fig. 2, distributions of "molecular" genetic variation on the x-axis are mapped into distributions of phenotypically expressed genetic variation on the y-axis. At each point, A, B, and C, the molecular variation is the same, but due to the epistasis the distributions of phenotypically expressed genetic variation are different. Over the range of variation at each point, the map is approximately linear, and fitting a statistical regression would support an approximately additive model at each point, so that the variation mapped to the phenotype axis would be additive genetic variation. Moving from point A to point B, the positive epistasis increases the additive variance, and moving on towards point C, the negative epistasis in this region would reduce the additive variance, and evolvability would disappear as complete canalization is approached. At each point during this trajectory the phenotypic response to selection could be predicted from the additive genetic variances, but the long-term dynamics would be determined by the effects of epistasis on the dynamics of the additive variance.

Even if the range of variation was sufficient to cover nonlinearities as in Fig. 3, the statistical epistasis would be estimated as deviations from the best-fitting linear
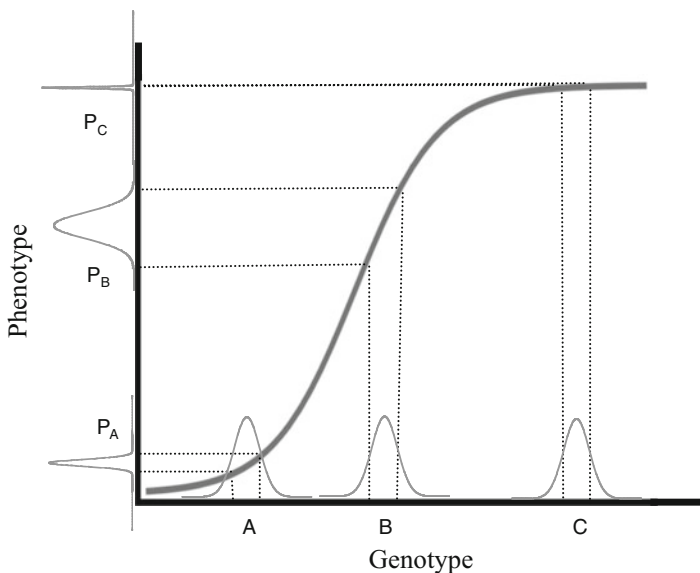
Fig. 2 The same levels of molecular genetic variation will generate different levels of variation in the phenotype depending on the genetic background (positions *A, B,* or *C*) (Modified from Hansen (2015))
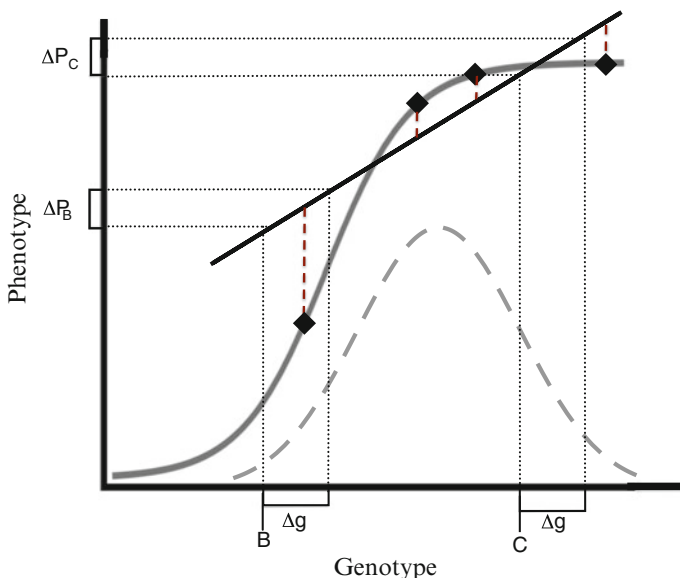
Fig. 3 Fitting an additive model (*straight black line*) over a range of genetic variation (*dashed-line distribution* along x-axis) captures the average effect, ΔP, of an allele substitution, Δg, over the range but also constrains the average effects to be constant so that $\Delta P_B = \Delta P_C$. Epistasis causes residual deviations from the linear model (*diamonds*), but their variance does not indicate specific patterns in the map

approximation and fail to describe the specific nonlinearities in the map. Epistatic variance could be detected, but it would be similar regardless of whether the biological epistasis was positive, negative, or simply random. The model would predict constant additive effects and evolvability over the range of the map.

A clear conceptual distinction between biological and statistical epistasis emerged gradually in the 1990s. In a key paper, Cheverud and Routman (1995) introduced the concept of "physiological" (= biological) epistasis and showed that it can influence the additive genetic variance. Hansen and Wagner (2001) developed this further and showed how "functional" (= biological) epistasis could be represented in a quantitative genetics framework. Carter et al. (2005) used Hansen and Wagner's multilinear representation of epistasis to formally describe the effects of biological epistasis on selection dynamics. In particular, they described how positive directional epistasis leads to the evolution of increasing additive variance and evolvability, while negative directional epistasis has the opposite effect. If the epistasis is nondirectional without any systematic patterns, the dynamics are almost indistinguishable from an additive model.

Such systematic effects of biological epistasis on the selection response have nothing to do with selection on epistatic variance. Selection on the epistatic variance leads to a buildup of linkage disequilibrium that is transient in the sense that it is rapidly broken down by recombination. In contrast, the effects of directional

epistasis are permanent, because they are mediated through changes in the genetic background that modify the biological effects of subsequent allele substitutions. If selection increases the frequency of alleles that, say, increase a trait, and these alleles have an average positive epistatic interaction with other alleles that have a positive effect on the trait, then these other alleles will more often find themselves in genetic backgrounds that elevate their effects. These elevated effects are permanent in the same sense as changes of allele frequencies are permanent.

Permanent effects of epistasis on the selection response were not captured by quantitative-genetics theory, because the statistical representation of epistasis as residuals from a regression constrained it to be nondirectional. The missing conceptual distinction between statistical and biological epistasis then led many to the inference that epistasis in general was unimportant (reviewed in Hansen 2013).

The NOIA model of Álvarez-Castro and Carlborg (2007) provides a general framework for representing most forms of functional (biological) and statistical epistasis and for translating between them.

Estimating Epistasis

In classical quantitative genetics, epistasis is estimated either as epistatic variance components inferred from patterns of resemblance between relatives or from line-cross analyses (Lynch and Walsh 1998). Line-cross analyses are based on regressions of the mean phenotypes of different crosses ("line-cross derivates") on the fraction of genes they have from each parental line and on their level of heterozygosity. For example, a back cross between the F1 and a parental is predicted to have 75% of its genes from this parental and 25% from the other and to be 50% heterozygotic. This allows the fitting of crude models of interaction between genes from the two parental lines. In principle, nonlinearities of the form illustrated in Fig. 1 can be inferred from such data, but classical line-cross analysis has yielded few insights due to its focus on significance testing rather than estimation and on the distinction between AA, AD, and DD types of epistasis. In any case, this method is now largely superseded by marker-assisted approaches.

Quantitative-trait locus (QTL) and genome-wide association studies (GWAS) use molecular markers to identify positions in the genome with effects on phenotypic traits. These approaches have been focused on identifying genes and estimating their individual effects, but it is possible to fit regression models with interactions that can identify epistasis (Lynch and Walsh 1998; Malmberg and Mauricio 2005). The detection of epistasis is made difficult by the large number of potential interactions and the use of significance thresholds to detect individual effects. Strong and systematic patterns of epistasis may go undetected, because they are spread over many interactions with individually small effects and there is a danger that significant interactions may be extremes that are atypical of the general patterns. Evidence for epistasis often comes from variants of these models in which larger ranges of phenotypes are studied (e. g., Huang et al. 2013).

The empirical study of epistasis has suffered from a lack of connection between statistical methods and theoretical relevance (Hansen 2015). The classical epistatic variance components have little evolutionary relevance, and the marker-based estimates are typically constrained to be nondirectional by the use of the standard statistical regression model. Le Rouzic (2014) reviews modifications and methods for detecting directional patterns of epistasis. There is also a tradition for studying theory-relevant patterns of epistasis on fitness, for example, by regressing fitness against correlates of accumulated mutations to estimate levels of synergistic epistasis among deleterious mutants. More recently, systematic studies of interactions between induced mutations on fitness and life-history traits in yeast and bacteria have been used to elucidate the role of epistasis in adaptation (e.g., Perfeito et al. 2014).

Epistasis Analysis in Molecular Genetics

In molecular genetics, epistatic interactions between, usually loss-of-function, mutations are used to infer the position of genes in a pathway. Following Bateson an epistatic mutation is a mutation that masks the effect of another (hypostatic) mutation, and this relationship is taken as evidence that the gene with the epistatic mutation is coming after the other in a pathway. The validity of this inference requires a number of auxiliary assumptions including the two mutations being the only factors affecting the phenotype. Drees et al. (2005) give a general overview of epistasis analysis.

More generally, the relationship between epistasis and the underlying structure of metabolic pathways, gene-regulatory networks, or physiological/developmental interactions is a topic of research in systems biology.

The Importance of Epistasis

The main relevance of epistasis for evodevo, at least, comes from its connection to the evolution of evolvability and canalization. It has only recently been recognized that this depends on systematic patterns of gene interaction that are not identifiable within the models of statistical genetics. Consequently, there is only scattered work to identify and formally describe how the many possible patterns of interaction and nonlinearity of the genotype-phenotype map may influence evolution. Beyond the identification of directional epistasis and convexity as key elements in the evolution of evolvability (e.g., Rice 1998; Carter et al. 2005), there is a body of work on how canalization may hide genetic variation that can subsequently be released in an evolutionary capacitance mechanism (e.g., Hermisson and Wagner 2004).

More generally, epistasis is related to the complexity of the genotype-phenotype map. It is here useful to distinguish between magnitude and sign epistasis. While sign epistasis refers to cases where a change in the genetic background would change the order of the effects of genotypes at a locus, magnitude (or order-preserving)

epistasis refers to cases where only the magnitude and not the order of effects are changed. Specifically, sign epistasis has been defined as a change in the ordering of fitness values, and this sets up the possibility of complex dynamics with the possibility of internal equilibria and multistability that may act as strong constraints on evolution (Weinreich et al. 2005). The existence of complex epistasis creating multipeaked genotype-fitness relations was a premise of Wright's view of evolution as expressed in his shifting-balance theory and contrasts with the Fisherian view of smooth additive landscapes (e.g., Whitlock et al. 1995). For Wright, evolution consisted in jumps between such peaks mediated by genetic drift in small sub-populations. A general model of the interaction between genetic drift and epistasis can be found in Barton and Turelli (2004).

One important question is whether patterns of epistasis may reflect limits to evolution. If a trait is selected up towards a limit, we may expect a pattern of negative epistasis where allele substitutions that increase the trait towards the limit show increasing canalization or even reversals of effect when the trait approaches the limit. Such epistatic constraints can in principle be investigated by studying the relationship between phenotypic trait values and the effects of allele substitutions, but this has of yet not received systematic attention. On the other hand, the existence of epistasis may also provide the possibility of breaking constraints by allowing pleiotropic effects to evolve (Pavlicev and Cheverud 2015).

The influence of epistasis increases with increasing distance in genotype space, and this makes it important in macroevolution and speciation. This is illustrated by the Bateson-Dobzhansky-Muller model for the evolution of postzygotic reproductive isolation. Even without differences in selection regime, isolated populations will experience different genetic changes due to genetic drift (e.g., systems drift). Such changes must be compatible with the genetic background in their own population, but there is no selection for compatibility with the genetic background of a different population, and hybridization will then generate individuals with untested gene combinations. Such combinations with deleterious effects on fitness are called Bateson-Dobzhansky-Muller incompatibilities. These will accumulate at an accelerating pace with increasing genetic difference between populations, and virtually guarantee that complete reproductive isolation will eventually arise as genetic distance is increasing.

Epistasis is a factor in the evolution of recombination and sexual reproduction. The costs and benefits of breaking up old and creating new allele combinations depend on the patterns of epistatic interaction among the alleles. While the breakup of coadapted gene complexes is unfavorable, it can be favorable to create offspring with diverse gene combinations to increase the probability that some of them are well adapted or free from combinations of deleterious alleles. If adaptation requires individually nonfavorable mutations in several genes, the rate of adaptation may be greatly elevated by sexual recombination. According to the deterministic-mutation hypothesis, sex is maintained as an adaptation to reduce the mutation load, but this works only in the presence of relatively strong *synergistic* epistasis where the fitness effects of several deleterious mutations are more severe than the (multiplicative) effects of the mutations in isolation.

Summary of Epistasis Terminology

The key distinction in epistasis terminology is between statistical epistasis, Fisher's epistacy, on one side, and what has variously been called biological, functional, or physiological epistasis on the other.

Statistical epistasis refers to the interaction terms in a least-squares regression on the presence of alleles. It can be divided into pairwise additive-by-additive (AA) and higher-order interactions. The variances explained by these interaction terms are the additive-by-additive epistatic variance, etc.

Hansen and Wagner (2001) defined functional epistasis as a dependency of the effects of a genetic substitution (on one or multiple loci) on the genetic background (i.e., the state of other loci in the genotype). This is the essence of the biological epistasis concepts including Cheverud and Routman's (1995) physiological epistasis, which was defined as a dependence of the difference in genotypic values at one locus on the state of another locus. The idea behind these concepts was to formally define epistatic effects independently of the composition of a population. They are still relative to a reference genotype, however, and specification of the reference genotype remains essential in all modeling of epistasis. Estimation and modeling of epistasis may be misleading if implicitly assumed reference genotypes are not made clear. Tools for translating between different reference genotypes and for relating biological and statistical epistasis are provided in Hansen and Wagner (2001), Barton and Turelli (2004), and Álvarez-Castro and Carlborg (2007).

Positive and negative epistasis refer to interactions for which the composite effect of two or more substitutions are elevated above or depressed below the sum of their individual effects. This requires a scale, and positive epistasis in one direction equals negative epistasis in the other. Systematic positive or negative interactions in one direction are called directional epistasis, while cases in which positive and negative interactions cancels out are called nondirectional epistasis. Magnitude epistasis or order-preserving epistasis is used when changes in the genetic background only cause changes in the magnitude of effects, while sign epistasis or order-breaking epistasis refer to cases in which the order of effects of the genotypes at a locus are changed. Multilinear epistasis refers to a pattern in which sets of genotypic effects are proportionally modified by changes in the genetic background.

The terminology for fitness epistasis is convoluted with positive and negative epistasis sometimes referring to interactions between beneficial (fitness-increasing) mutations and sometimes to interactions between deleterious (fitness-decreasing) mutations. In addition, terms such as synergistic, antagonistic, and diminishing-returns epistasis are used for positive or negative fitness interactions in either direction. It is also essential to distinguish between Wrightian fitness where epistasis is usually defined as deviations on a multiplicative scale and Malthusian fitness where it is usually defined as deviations on an arithmetic scale (Wagner 2010). Fitness epistasis may also differ depending on whether the reference genotype is one with maximal or average fitness. Furthermore, epistasis for fitness must be distinguished from epistasis in the traits underlying fitness. Unless the fitness function is

linear, these will differ, and with a nonlinear (e.g., stabilizing) fitness function, an additive genetic architecture in the trait will generate systematic epistasis for fitness.

The widespread relevance of gene interaction has given rise to many context-dependent terminologies including the Bateson-Dobzhansky-Muller incompatibilities for deleterious fitness interactions between alleles from different populations, the concept of a modifier where one gene is assumed to change the effect of another without itself having an effect on the trait, the concept of differential epistasis when pleiotropic effects are differentially modified by a change in the genetic background, and the concept of compensatory change where the effect of one substitution is nullified by another.

Cross-References

▶ Canalization: A Central but Controversial Concept in Evo-Devo
▶ Evolvability
▶ Pleiotropy and Its Evolution: Connecting Evo-Devo and Population Genetics
▶ Variational Approaches to Evolvability: Short- and Long-Term Perspectives

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