doi:10.1111/evo.12214

WHY EPISTASIS IS IMPORTANT FOR SELECTION AND ADAPTATION

Thomas F. Hansen[1,2]

[1]*Department of Biology, University of Oslo, CEES P.O. Box 1066, Blindern, N-0316 Oslo, Norway*

[2]*E-mail: Thomas.Hansen@bio.uio.no*

Received March 25, 2013
Accepted July 4, 2013

Organisms are built from thousands of genes that interact in complex ways. Still, the mathematical theory of evolution is dominated by a gene-by-gene perspective in which genes are assumed to have the same effects regardless of genetic background. Gene interaction, or epistasis, plays a role in some theoretical developments such as the evolution of recombination, reproductive isolation, and canalization, but is strikingly missing from our standard accounts of phenotypic adaptation. This absence is most puzzling within the field of quantitative genetics, which, despite its polygenic perspective and elaborate statistical representation of epistasis, has not found a single important role for gene interaction in evolution. To the contrary, there is a widespread consensus that epistasis is evolutionary inert, and that all we need to know to predict evolutionary dynamics is the additive component of the genetic variance. This view may have roots in convenience, but also in theoretical results showing that the response to selection derived from epistatic variance components is not permanent and will decay when selection is relaxed. I show that these results are tied to a conceptual confusion, and are misleading as general statements about the significance of epistasis for the selection response and adaptation.

KEY WORDS: **Gene interaction, genotype–phenotype map, quantitative genetics, selection response.**

Recent large-scale QTN and genome-wide association studies show that quantitative traits are typically affected by large numbers of genes with individually small effects (e.g., Flint and Mackay 2009; Rockman 2012), and there is accumulating evidence for extensive interactions and dependency of effects on genetic background (Malmberg and Maurizio 2005; Phillips 2008; Shao et al. 2008; Flint and Mackay 2009; Zwarts et al. 2011; Zuk et al. 2012; Huang et al. 2013). What this means is that there is extensive evidence for what has variously been called physiological (Cheverud and Routman 1995), functional (Hansen and Wagner 2001a; Álvarez-Castro and Carlborg 2007), or biological (Moore and Williams 2005) epistasis. This defines epistasis in terms of a dependency of the phenotypic effects of gene substitutions on the genetic background, and is thus a representation of gene interaction that is different from the statistical representation in classical quantitative genetics (e.g., Lynch and Walsh 1998). Although "functional epistasis," as I will call it here, is a descriptor of the genotype–phenotype map that is conceptually independent of population variation, the "statistical epistasis" derives from statistical regression of phenotype on gene content and reflects the importance of gene interactions in explaining segregating variation within a population.

With explicit "functional" models of the genotype–phenotype map, theoreticians have discovered many roles for epistasis in evolutionary dynamics driven by natural selection. These include crucial roles in the evolution of sex and recombination (e.g., Maynard Smith 1978; Kondrashov 1988; Burt 2000), which are based on an influence of epistasis on the mutation load (Kimura and Maruyama 1966; Charlesworth 1990; Hansen and Wagner 2001b), on the operation of Muller's ratchet (Butcher 1995; Lynch et al. 1995), on the inbreeding load (Charlesworth 1998), and on the evolution of recombination rates (e.g., Kimura 1956; Barton 1995; Otto and Barton 2001). Epistasis plays important roles in various models of speciation (Templeton 1981; Gavrilets 2004), and is essential for the evolution of postzygotic reproductive isolation (Orr 1995; Johnson 2000; Orr and Turelli

EVOLUTION
INTERNATIONAL JOURNAL OF ORGANIC EVOLUTION

2001; Gavrilets 1999, 2003, 2004; Coyne and Orr 2004; Fierst and Hansen 2010; Bank et al. 2012). It affects transgressive hybridization (Rieseberg et al. 1999; Barton 2001), and is a prerequiste for the evolution of coadapted gene complexes (e.g., Templeton 2000; Haag 2007). Epistasis is essential for the evolution of canalization and genetic robustness (Wagner et al. 1997; Rice 1998, 2002, 2004; Kawecki 2000; Hermisson et al. 2003; Flatt 2005; Wagner 2005; Hansen et al. 2006; Le Rouzic et al. 2013), and in the evolution of genetic architecture more generally (reviewed in Bagheri 2006; Hansen 2006, 2011). It influences the maintenance of genetic variation under stabilizing selection with mutation (Hermisson et al. 2003; Le Rouzic et al. 2013) and the evolution of genetic polymorphism (e.g., Karlin 1975; Gimelfarb 1989; Zhivotovsky and Gavrilets 1992; Gavrilets 1993). It has also long been argued that epistasis may play a fundamental role in shaping "Wrightian" adaptive landscapes by generating complex fitness peaks and paths (e.g., Kauffman 1993; Whitlock et al. 1995; Weinreich 2005; Weinreich et al. 2005), and this makes it an essential component in the shifting-balance theory of evolution (e.g., Wright 1977, ch. 13). Finally, it has been shown both analytically and with simulations that functional epistasis can have strong and varied effects on the response to directional selection on both short and long time scales (Keightley 1996; Carter et al. 2005; Hansen et al. 2006; Hallander and Waldemann 2007; Yukilevich et al. 2008).

In contrast, quantitative geneticists working with the statistical representation of epistasis have hardly discovered any significant role for gene interaction in evolution. This is not because it has been ignored. After all, epistasis is deeply integrated into the quantitative genetics models for predicting similarities between relatives, but the wide-spread misconception that it has no permanent effects on selection dynamics has restricted the search for influence to nonselective mechanisms, and although a substantial literature developed around the possibility that epistatic variance can interact with genetic drift to increase additive variance during population bottlenecks (e.g., Goodnight 1988; Cheverud and Routman 1996; Barton and Turelli 2004), the potential effects seem insignificant compared to the systematic changes that can be caused by selection (Hansen and Wagner 2001a; Turelli and Barton 2006; see also Houle et al. 2011).

The contrast between the functional and statistical representations of epistasis is most striking in the different predictions they induce about the role of epistasis in the response to selection. While it has been shown that systematic patterns of functional epistasis are important (e.g., Carter et al. 2005), the general consensus in the quantitative genetics literature is that epistasis has small and transient effects on the selection response (e.g., Bulmer 1980; Hill et al. 2008; Crow 2008, 2010), and interactions between epistasis and selection go essentially unmentioned in all leading quantitative genetics textbooks (e.g., Falconer and Mackay 1996; Roff 1997). How can this be? I will first explain how functional epistasis influences selection dynamics and then discuss why this influence has been overlooked in the classical quantitative genetics literature.

The Effects of Functional Epistasis on the Selection Response

Why epistasis should affect the selection response is easy to understand in a nontechnical manner. Functional epistasis is defined as a dependency of the effects of gene substitutions on genetic background. If selection changes the frequency of alleles at some locus X, then this will change the phenotypic effects of alleles at any epistatically interacting locus, Y. This means that subsequent allele frequency changes at locus Y will have different phenotypic effects than they would have had before the changes at locus X. Note that these effects are not transitory, but permanent in the same sense as any other effect of allele frequency change is permanent. Because of the symmetry of epistasis, such changes tend to be reinforcing. Further changes at locus Y will change the phenotypic effects of alleles in locus X, and this sets up feedback loops with the potential for profound changes of selection dynamics.

From this description it is obvious that the type of epistasis will matter. We can distinguish four scenarios: (1) If there are systematic positive epistatic interactions between genes such that gene substitutions that have positive effects on the trait also tend to increase the effects of other potential gene substitutions with positive effects on the trait, then we will get a systematic increase of the phenotypic effects of gene substitutions under directional selection. This will elevate additive genetic variance, and support an accelerating response to selection; (2) if there are systematic negative epistatic interactions such that gene substitutions that have positive effects on the trait tend to decrease the effects of other potential gene substitutions with positive effects, then additive variance will decrease and the response to selection will decelerate; (3) if there is epistasis without any systematic direction of interaction, then some gene substitution effects will increase and some will decrease, but the net change will be zero, and the response to selection will resemble that of an additive system; and (4) if negative epistasis is sufficiently strong or if different alleles at a locus have different specific interactions with the background, then the order of allelic effects may change, and we get complex dynamics with the possibility of polymorphic and alternative equilibria, as well as the making and breaking of canalized constraints.

As a simple qualitative illustration, I analyze a two-allele, two-locus model with epistasis in the Appendix. The model is

modified from Kimura (1965), and was used by Crow and Kimura (1970) to show how the selection response was nearly perfectly predicted by the additive variance with no effects of statistical epistasis. As demonstrated in Figure 1, this does not mean that functional epistasis is unimportant. We can see both an accelerated response with positive epistasis and a decelerated response with negative epistasis. Figure 2 illustrates how the effects of epistasis are permanent and only minimally influenced by transitory changes in linkage disequilibrium.

Such dynamics are equally present in polygenic systems. Carter et al. (2005) derived analytical equations to describe the response to linear selection as a function of patterns of epistasis. Their analysis was based on the multilinear model of Hansen and Wagner (2001a) in which the key assumption is that a gene substitution can change the phenotypic effect of any other gene or genotypic substitution, but only as a linear function of its own phenotypic effect. This allows change in magnitude, but preserves the order of the effects of the genotypes at a locus except for the possibility of a global flip. Hence, this is primarily a model of what has variously been called order-preserving or monotonic epistasis (Weinreich et al. 2005; Gjuvesland et al. 2011). Ignoring the effects of linkage disequilibrium, Carter et al. (2005) found that the first terms of the equations for the per generation changes in the trait mean, $\bar{z}$, and the additive variance, V_A, are

$$\Delta\bar{z} = \beta V_A + \tfrac{1}{2}\bar{\varepsilon}\,(\beta V_A)^2 + \cdots, \qquad (1A)$$

$$\Delta V_A = 2\beta \sum\nolimits_i {}^iC_3 - 2\beta^2 \sum\nolimits_i {}^iC_2^2 + 2\beta\bar{\varepsilon}V_A^2 + \cdots, \qquad (1B)$$

where β is the selection gradient, ${}^iC_2$ and ${}^iC_3$ are the second and third cumulant of allelic (reference) effects at locus i, summations are over all loci, and $\bar{\varepsilon}$ is a parameter describing the directionality of epistasis. Inspecting these equations, we can see that the change in the trait mean is affected by epistasis, but this effect is generally small and second order in the strength of selection, and Carter et al. (2005) also found that it tends to be counteracted by the dynamics of linkage disequilibrium making the additive prediction for the single-generation change in the trait mean nearly perfect. The importance of epistasis is mediated through changes of the additive variance (and of higher moments, which we will not consider here). The first two terms in equation (1B) are the standard terms we also find in an additive model describing how changes in additive variance depend on the skew and squared variance of the allelic-effect distributions at individual loci (Bürger 2000). The third term describes the leading effect of epistasis. The parameter $\bar{\varepsilon}$ is a weighted average of epistasis coefficients describing the interaction between pairs of loci (see Carter et al. 2005 for details). A positive value indicates positive directional epistasis, and a negative value indicates negative directional epistasis. The equations thus formalize our verbal description above of how systematic positive patterns of epistasis support the evolution of increasing

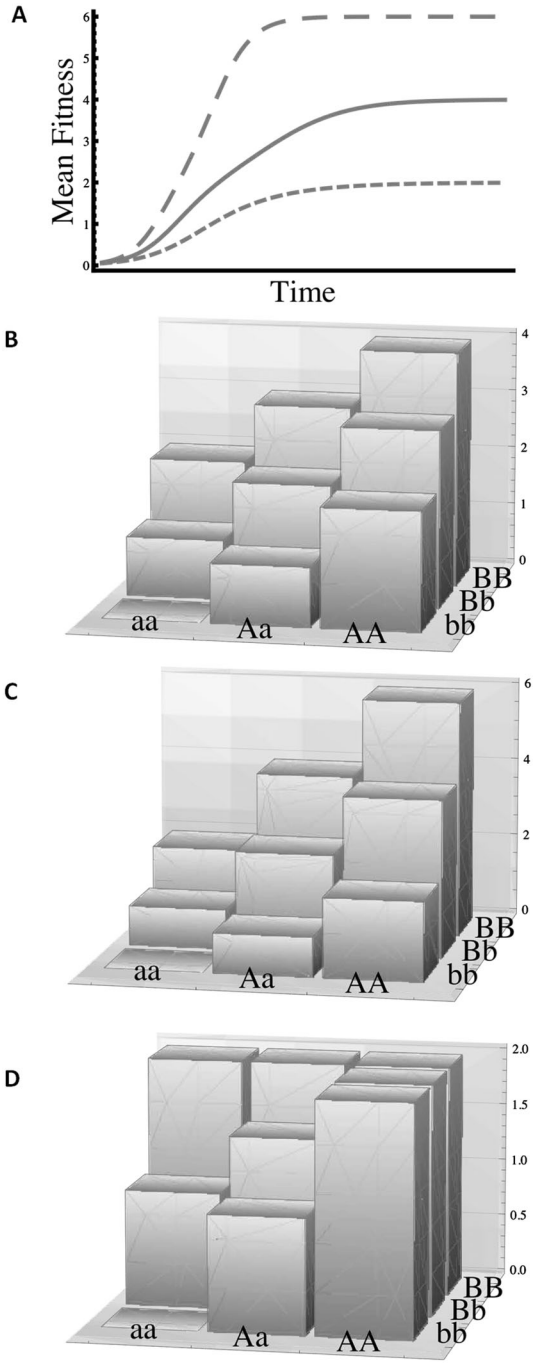

Figure 1. **Evolutionary dynamics of a two-locus epistatic model. (A) Shows the time dynamics of mean Malthusian fitness for three different genotype–phenotype maps illustrated in (B–D). The whole line gives the dynamics of the additive genotype–phenotype map shown in (B), the coarsely dashed line shows the dynamics of the positively epistatic map in figure (C; $\varepsilon = 0.5$), and the finely dashed line shows the dynamics of the negatively epistatic map in (D; $\varepsilon = -0.5$). The shown dynamics are with free recombination ($r = 0.5$) and random mating. The starting haplotype frequencies were 0.98 for ab, 0.01 for Ab and 0.005 for aB and AB. Based on numerical integration of dynamical equations given in the Appendix. Further parameter values and discussion of their meaning are given in the Appendix.**

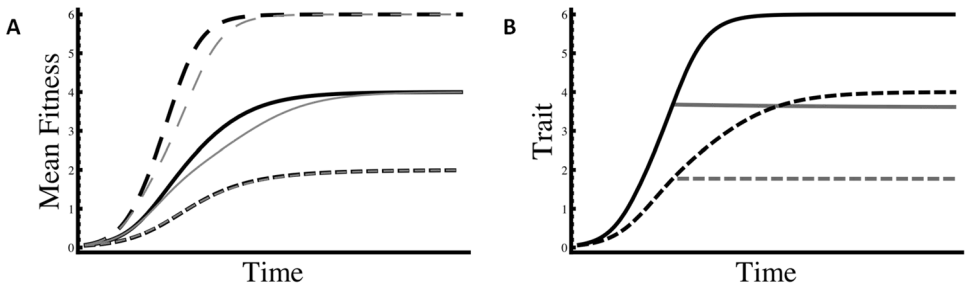

Figure 2. **Effects of linkage disequilibrium. (A) Illustrates the (small) effects of strong linkage. The black lines show the same models as in Figure 1, but with recombination rate $r = 0.01$. The grey lines show the same models with free recombination for comparison. (B) Illustrates how almost all the effect of epistasis is permanent. The black lines show the dynamics of the additive (whole line) and positive epistatic (dashed line) models as in Figure 1, but with $r = 0.25$. The grey lines show the dynamics with selection relaxed. Note how the difference between the epistatic and the additive model remains unchanged after selection is relaxed. There is a minute temporary change due to decay of linkage disequilibrium, which has almost reached zero at the end of the simulation, but this is too small to be apparent in the graph. Other parameters are as in Figure 1.**

additive variance and subsequently faster evolution of the trait mean, whereas a systematic pattern of negative epistasis has the opposite effect. Carter et al. (2005) show that effects of directional epistasis on the skew (the third cumulants) of allelic distributions may also be very important, and that this to some extent counteract the direct effect on the variance. Still, a genetic architecture with significant directional epistasis will rapidly deviate from the additive prediction. As also illustrated for our two-locus model in Figure 2A, linkage and hence linkage disequilibrium have small effects on this dynamics.

As time extends, the effects of epistasis become more and more important and complex. There will be increasing influence of higher-order directional and other forms of patterned epistasis (see Carter et al. 2005 for details). Loci with a predominance of negative epistatic interactions will also become increasingly canalized, and eventually experience a flip or sign change in the order of effects, which can boost evolvability (Hansen et al. 2006). This may be viewed as a mathematical peculiarity of the multilinear model and permanent canalization of such loci may be more biologically realistic, but it illustrates the complexities that may result when epistasis is not order preserving. Some effects of sign epistasis in our two-locus model are illustrated in Figure 3.

A key point is that it is not the presence of epistasis per se that matters, but the presence of particular patterns of epistasis. If epistasis is nondirectional ($\bar{\varepsilon} = 0$, and there are no other patterns in the interactions), then the system is predicted to behave identically to an additive system. Simulations in Carter et al. (2005) and Hansen et al. (2006) show that this prediction can hold true for hundreds of generations, although small deviations from perfect symmetry will eventually make the system diverge from additive behavior. Note also that nondirectional trait epistasis will generate directional epistasis for fitness whenever the fitness function is not linear, and almost any type of epistasis will influence evolutionary dynamics under stabilizing or fluctuating selection (e.g., Hermisson et al. 2003; Le Rouzic et al. 2013).

The classical variance components of statistical epistasis are uninformative about such dynamics, because they do not distinguish between the relevant patterns of epistasis. To illustrate, Hansen and Wagner (2001a) showed that the additive-by-additive epistatic variance is given approximately under the multilinear model by the equation

$$V_{AA} = \tfrac{1}{2}\overline{\varepsilon^2}V_A^2, \tag{2}$$

where $\overline{\varepsilon^2}$ is a weighted average of the squares of the epistasis coefficients mentioned earlier. Even if these coefficients average to 0 ($\bar{\varepsilon} = 0$), so that there is no directional epistasis, an average of their squares is not 0 unless (pairwise) epistasis is totally absent. Hence, the presence of the additive-by-additive epistatic variance can be consistent with elevated, diminished, or no effect on the selection response. Therefore, it has no predictive value. Similar considerations apply to all other epistatic variance components (their relation to functional epistasis is detailed in Hansen and Wagner 2001a). Beyond the multilinear model, these variance components also cannot distinguish between order-preserving and order-breaking epistasis, and are therefore uninformative about the profound dynamical consequences of this distinction.

Why did the Classical Analysis Miss the Importance of Epistasis?

In the classical quantitative genetics literature, the genotype–phenotype map is represented by the statistical regression model developed by Fisher (1918), Cockerham (1954), and Kempthorne (1954). This model regresses the phenotype on "gene content" and epistasis appears as statistical interaction terms. Although

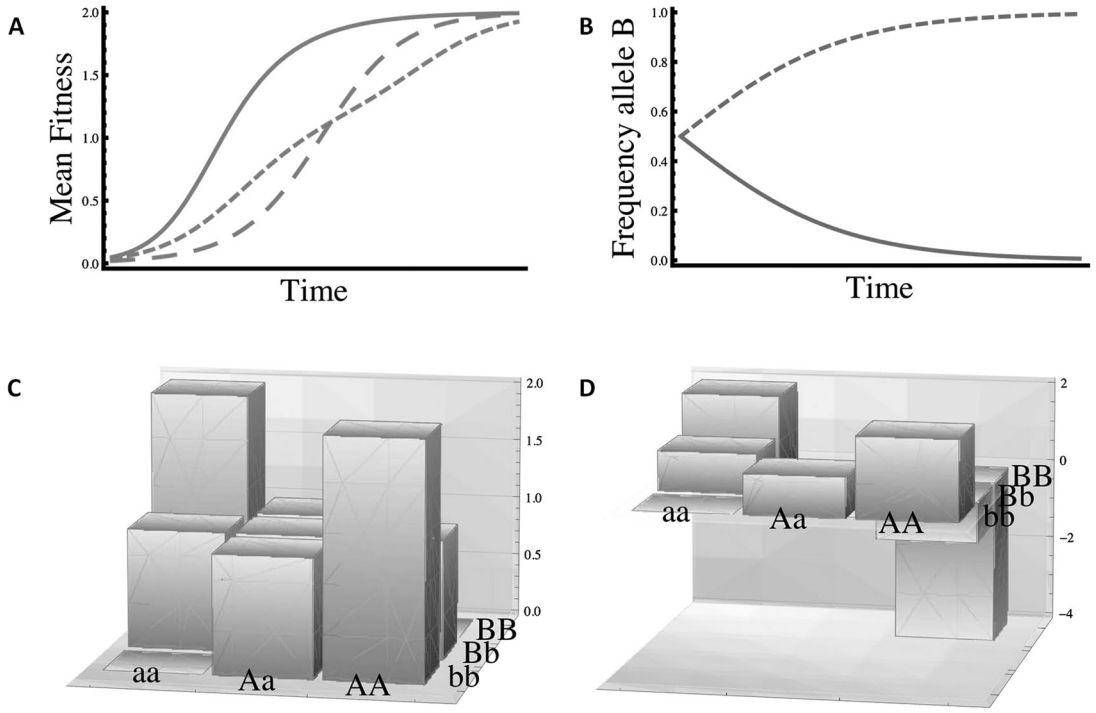

Figure 3. **Sign epistasis. (A) Shows some examples of dynamics with sign epistasis, and (B) illustrates how allele B may either go to fixation (dashed line) or be lost (whole line) depending on whether allele A or allele a has been fixed on the other locus. For comparison with Figure 1 the whole line in (A) shows the case with $\varepsilon = -0.5$, the architecture illustrated in Figure 1D, the coarsely dashed line is with $\varepsilon = -1$, as illustrated in (C), and the finely dashed line is with $\varepsilon = -2$ as illustrated in (D). The model in (B) is with $\varepsilon = -1$. Other parameters are as in Figure 1.**

the variance components associated with these interaction terms have now been supplemented with direct estimates of interaction coefficients in marker-based analyses, the underlying model is similar. Until recently there were no serious attempts at relating this model to functional (biological) representations of epistasis.

A key property of this model is that of orthogonality, which ensures that the different variance components are statistically independent and can be consistently estimated from models including different components. Orthogonality is based on defining the effects of alleles or of combination of alleles as deviations from a population mean (Álvarez-Castro and Carlborg 2007). It is important to realize that orthogonality does not ensure that the variance components are biologically independent. It gives no license for treating the variance components as biologically independent parameters that can be varied and studied independently of each other.

One of the most commonly cited arguments for the non-importance of epistasis in selection dynamics are the findings by Griffing (1960) that although some epistatic effects are transferred from parents to offspring, the changes due to selection on these are transient in the sense that they are due to a buildup of linkage disequilibrium that will decay if selection is relaxed (see also Bulmer 1980, pp. 160–162). Griffing built his argument on the classical variance decomposition of the total phenotypic variance as

$$V_P = V_A + V_D + V_{AA} + \cdots, \tag{3}$$

where V_A is the additive genetic variance, V_D is the dominance variance, V_{AA} is the additive-by-additive epistatic variance, etc. Griffing observed that one fourth of the additive-by-additive variance is transferred from parent to offspring (in the sense of contributing to the covariance between them). He then considered the effect of selection on the additive-by-additive component assuming that this could be studied independently of the other components, and that the results for the different genetic components could be added together. By definition selection on additive-by-additive genetic deviations cannot alter allele frequencies, because the interaction terms are defined to be independent of allelic effects (i.e., orthogonal). In other words, any phenotypic effect of allele-frequency change is by definition a part of the additive variance. The only thing that can change is the frequencies of co-occurrence of alleles, that is the linkage disequilibrium. Selection on epistatic deviations thus only has the effect of increasing the frequency of co-occurrence of beneficial allele combinations above the frequency changes due to average effects of the alleles

in isolation. Because linkage disequilibrium is continuously broken down by recombination this change is "transitory" and "not permanent."

In his analysis, Griffing assumed that the additive genetic variance stayed constant (e.g., Griffing 1960, p. 327). This automatically removes the systematic, cumulative, and permanent effects of epistasis that were identified by Carter et al. (2005). Griffing's analyses are correct as statements about the effects of epistatic variance on selection response due to changes in linkage disequilibrium, but they cannot be taken as statements about the general effects of epistasis on the response to selection. Griffing and other quantitative-genetics theoreticians were certainly aware that the additive genetic variance may change under selection (the two first terms in equation 1B are a standard part of quantitative genetics theory), but their conceptualization of epistasis as independent variance components precluded them from asking how functional gene interactions may influence these changes. More seriously, the missing distinction between functional and statistical epistasis invited an overgeneralization of the results. The results derived for the statistical epistatic variance components were implicitly assumed to be results about epistasis in general (as in Hill et al. 2008).

Kimura (1965) analyzed a two-locus model similar to the one in the Appendix (see also Kimura 1956; Lewontin and Koijma 1960; Felsenstein 1965). He showed that as long as epistasis for fitness is not too strong relative to the recombination rate, the system settles into a "quasi linkage equilibrium" in which the degree of linkage disequilibrium stays constant and the rate of change of mean fitness is equal to the additive variance in fitness and unaffected by the level of epistatic variance (but see Karlin 1975 for criticism). Kimura (1965) did not assume that the additive variance stays constant in his model. In fact, his numerical examples (his Tables 1 and 4), show huge changes in the additive variance. As illustrated by my reanalysis, such changes are influenced by the strength and direction of the epistatic interaction, and neither Kimura's nor Crow and Kimura's (1970) analysis of this model imply that functional epistasis is unimportant under directional selection. Hence, the claims by Crow (2008, 2010) that this result implies we can ignore the effects of epistasis on the selection response are only correct in a highly restricted sense, and totally misleading as general statements about evolutionary dynamics over many generations.

There were many studies of selection on epistatic two-locus systems in the older theoretical population genetics literature, but these were motivated by interests in polymorphic equilibria and the dynamics of linkage disequilibrium (reviewed in Wright 1969, ch. 4; Karlin 1975). In this context, effects of epistasis on allele-frequency changes were a nuisance and investigators often chose symmetrical setups in which the effects on allele-frequency dynamics were small (see, e.g. Lewontin and Koijma 1960). Even if permanent effects of epistasis were noted, at least in the sense of creating alternative equilibria and as deviations under strong selection, the cumulative effects of directional epistasis seem to have gone unnoticed. Later, Nagylaki (1992, 1993) and Turelli and Barton (1994) developed general models of polygenic dynamics under selection that also allow for epistasis, but they did not consider patterned epistasis and did not investigate the potentially cumulative nature of the effects. Dynamical effects of epistasis have been noted in models of metabolic control (Keightley 1996), and were of course implied in studies of canalization and of the various genetic loads mentioned earlier, but the inconsistency between this and the quantitative-genetics literature was never resolved.

The effects of epistasis on the selection response have also been explored in numerical simulation studies dating back to the 1960s. Some of these studies are based on additive sets of identical two-locus models, where epistasis is necessarily directional. Consequently, there were large effects of epistasis on the dynamics. For example, Young (1967), in an for the time impressively extensive set of simulations, found clear effects of epistasis on the response, concluding among other things that the heritability is a poor predictor of the response in the presence of epistasis. He did not, however, attempt to explain why this happened. This is also true for similar studies in which effects of epistasis can be gleaned from the results (e.g., Mueller and James 1983; Fuerst et al. 1997; Jannink 2003). In a more recent numerical study, Hallander and Waldmann (2007) found strong effects of epistasis on the selection response and noted the relation to patterns of functional epistasis.

In conclusion, the quantitative geneticists of the preceding century overlooked the permanent effects of epistasis due their reliance on a statistical representation of epistasis that did not capture the right aspects of gene interactions. The fact that the response to selection in one generation is well predicted by the additive genetic variance was taken to mean that epistasis is inconsequential. I conjecture that the reason why this happened was because the orthogonality of the genetic variance components was implicitly thought to imply that they were also biologically noninteracting. The explicit theoretical results showing that epistatic variance did not have permanent effects on the selection response were therefore thought to exclude any effect of epistasis in selection dynamics. Ultimately, this largely implicit chain of faulty reasoning was facilitated by the missing distinction between functional and statistical epistasis. Although this distinction has its roots in an understanding of the context dependency of (additive) gene effects (e.g., Lewontin 1974, ch. 6; Moreno 1994; Wagner et al. 1998; Templeton 2000), it was only toward the end of the century that quantitative geneticists started to consider the effects of (functional) epistasis on the additive variance (e.g., Goodnight 1987, 1988; Cheverud and Routman 1996), and we could start to

resolve the inconsistencies and develop the tools to investigate the full impact of epistasis in quantitative genetics (e.g., Rice 1998, 2002, 2004; Wagner et al. 1998; Hansen and Wagner 2001a; Barton and Turelli 2004; Carter et al. 2005; Demuth and Wade 2005; Álvarez-Castro and Carlborg 2007; Jannink et al. 2009; Pavlicev et al. 2010, 2011; Álvarez-Castro and Yang 2011; Gjuvesland et al. 2011; Álvarez-Castro et al. 2012a; Slatkin and Kirkpatrick 2012).

Is Epistasis Important?

Although I hope the theoretical objections to an influence of epistasis in selection and adaptation can now be put to rest, it does not automatically follow that epistasis is empirically important. Its domain of relevance has to be delineated by empirical means. We have seen that the potential influence of epistasis depends on genetical details about which we currently know little. On one hand, the situation is akin to the debate on the maintenance of genetic variation in mutation-selection balance, where model predictions depend on genetic details that are unobservable in practice (Turelli 1984; Barton and Turelli 1989), and this is even before the complexities of epistasis were added to the picture (Hermisson et al. 2003). On the other hand, we have also seen that there are some qualitative predictions about the effects of recognizable patterns of epistasis, such as positive or negative directionality. Further theoretical work may produce more testable hypotheses; for example, in relation to types of sign epistasis or patterns of multivariate directionality (see Pavlicev et al. 2011).

The perceived inertness of epistasis must have discouraged empirical investigations, but some information has accumulated. An important example demonstrating the impact of epistasis in artificial selection is the detailed analysis by Carlborg et al. (2006; Le Rouzic et al. 2008; Álvarez-Castro et al. 2012b) of the selection response in lines of chicken selected up or down for body size over 42 generations. Here it was shown that what was originally thought to be the effects of a major locus was in fact a system of four epistatically interacting loci, and that this architecture had mediated a considerably larger selection response than would have been expected without epistasis. There are also many examples of directional epistasis from line crosses between selected lines, which is an indication that it has influenced the selection response. This is made explicit in the analysis of selected mouse lines by Pavlicev et al. (2010), who showed the selected difference was influenced by (negative) epistasis (see also Ungerer et al. 2003; Le Rouzic et al. 2011; Pavlicev et al. 2011). Evidence for the adaptive value of epistasis can also be inferred from line-cross studies of natural populations with different local adaptations (e.g., Bradshaw and Holzapfel 2000; Fenster and Galloway 2000; and other contributions in Wolf et al. 2000; see also Bradshaw et al. 2005; Kelly 2005; Carroll 2007). In such studies, the influence of epistasis is commonly attributed to an interaction with a bottleneck or events early in the divergence of the populations. I suggest it is more likely with a direct interaction between epistasis and selection as described earlier. In general, reanalysis of more artificial selection lines and studies of the genetic basis of local adaptation with an eye to epistasis will be necessary to understand what impact epistasis may have had on adaptation.

It is perfectly possible that epistasis is often unimportant either because there is little epistasis in the first place or because it is largely nondirectional. After all, there is a widespread notion that the additive model is quite successful in accounting for variation and response to selection. For example, Hill et al. (2008) recently argued against the relevance of epistasis based on theoretical and empirical arguments that most variance should be additive (and also citing Griffing 1961). This reasoning fails to distinguish statistical and functional epistasis, and even if they were right that epistatic variance components are often small, this does not rule out the possibility of strong functional epistasis in the genotype–phenotype map. In effect, the classical quantitative genetics model resembles a Taylor approximation of the genotype–phenotype map. When there is little variation, the linear (additive) part fits well and explains most of the variance, but as the level of variation increases, the nonlinear (dominance and epistatic) parts become relatively more and more important and will explain larger and larger fractions of the variance (Moreno 1994; Hansen et al. 2011; and eq. 2). Hence, in situations in which selection causes large genetic changes, nonlinearity in the form of functional epistasis can generate large changes in gene effects and selection dynamics even if the genetic variance was nearly additive in the beginning and remained so at each step of the process.

Conclusions

Current theory makes it clear that functional epistasis is potentially important for understanding the response to selection. The impact of epistasis is negligible for the response of the trait mean over a single generation, but may increase exponentially with time and magnitude of change. It is important to obtain empirical estimates of the size and type of epistasis that determines these exponential effects, so as to know when epistasis can and cannot be ignored. Both theoretical and empirical work on epistasis should shift focus from the largely irrelevant and hard to estimate epistatic variance components of classical quantitative genetics and toward the study of systematic patterns of functional epistasis in the genotype–phenotype map. A good understanding of the potential influence of epistasis on short-time evolutionary dynamics is a necessary basis for understanding its essential role in macroevolutionary dynamics.

ACKNOWLEDGMENTS

I thank J. Álvarez-Castro, I. Gordo, and three reviewers for helpful comments on the manuscript.

LITERATURE CITED

Álvarez-Castro, J. M., and Ö. Carlborg. 2007. A unified model for functional and statistical epistasis and its application in quantitative trait loci analysis. Genetics 176:1151–1167.

Álvarez-Castro, J. M., and R.-C. Yang. 2011. Multiallelic models of genetic effects and variance decomposition in non-equilibrium populations. Genetica 139:119–1134.

Álvarez-Castro, J. M., Ö. Carlborg, and L. Rönnegård. 2012a. Estimation and interpretation of genetic effects with epistasis using the NOIA model. Methods Mol. Biol. 871:191–204.

Álvarez-Castro, J. M., A. Le Rouzic, L. Andersson, P. B. Siegel, and Ö. Carlborg. 2012b. Modeling of genetic interactions improves prediction of hybrid patterns—a case study in domestic fowl. Genet. Res. Camb. 94:255–266.

Bagheri, H. C. 2006. Unresolved boundaries of evolutionary theory and the question of how inheritance systems evolve: 75 years of debate on the evolution of dominance. J. Exp. Zool. 306B:329–359.

Bank, C., R. Bürger, and J. Hermisson. 2012. The limits to parapatric speciation: Dobzhansky–Muller incompatibilities in a continent-island model. Genetics 191:845–863.

Barton, N. H. 1995. A general model for the evolution of recombination. Genet. Res. 65:123–144.

———. 2001. The role of hybridization in evolution. Mol. Ecol. 10:551–568.

Barton, N. H., and M. Turelli. 1989. Evolutionary quantitative genetics: how little do we know? Ann. Rev. Genet. 23:337–370.

———. 2004. Effects of genetic drift on variance components under a general model of epistasis. Evolution 58:2111–2132.

Bradshaw, W. E., and C. M. Holzapfel. 2000. The evolution of genetic architectures and the divergence of natural populations. Pp. 245–263 *in* J. B. Wolf, E. D. Broodie, and M. J. Wade eds. Epistasis and the evolutionary process. Oxford Univ. Press, Oxford, U.K.

Bradshaw, W. E., B. P. Haggerty, and C. M. Holzapfel. 2005. Epistasis underlying a fitness trait within a natural population of the pitcher-plant mosquito, *Wyeomyia smithii*. Genetics 169:485–488.

Bulmer, M. G. 1980. The mathematical theory of quantitative genetics. Claredon, Oxford, U.K.

Bürger, R. 2000. The mathematical theory of selection, recombination, and mutation. Wiley, Chichester, U.K.

Burt, A. 2000. Perspective: sex, recombination, and the efficacy of selection—was Weismann right? Evolution 54:337–351.

Butcher, D. L. 1995. Muller's ratchet, epistasis and mutation effects. Genetics 141:431–437.

Carlborg, Ö., L. Jacobson, P. Åhgren, P. Siegel, and L. Andersson. 2006. Epistasis and the release of genetic variation during long-term selection. Nat. Genet. 38:418–420.

Carroll, S. P. 2007. Brave new world: the epistatic foundations of natives adapting to invaders. Genetica 129:193–204.

Carter, A. J. R., J. Hermisson, and T. F. Hansen. 2005. The role of epistatic gene interactions in the response to selection and the evolution of evolvability. Theor. Popul. Biol. 68:179–196.

Charlesworth, B. 1990. Mutation-selection balance and the evolutionary advantage of sex and recombination. Genet. Res. 55:199–221.

———. 1998. The effect of synergistic epistasis on the inbreeding load. Genet. Res. 71:85–89.

Cheverud, J. M., and E. J. Routman. 1995. Epistasis and its contribution to genetic variance components. Genetics 139:1455–1461.

———. 1996. Epistasis as a source of increased additive genetic variance at population bottlenecks. Evolution 50:1042–1051.

Cockerham, C. C. 1954. An extension of the concept of partitioning hereditary variance for analysis of covariances among relatives when epistasis is present. Genetics 39:859–882.

Crow, J. F. 2008. Maintaining evolvability. J. Genet. 87:349–353.

———. 2010. On epistasis: why it is unimportant in polygenic directional selection. Philos. Trans. R. Soc. B 365:1241–1244.

Crow, J. F., and M. Kimura. 1970. An introduction to population genetics theory. Harper & Row, New York, NY.

Demuth, J. P., and M. J. Wade. 2005. On the theoretical and empirical framework for studying genetic interactions within and among species. Am. Nat. 165:524–536.

Falconer, D. S., and T. F. C. Mackay. 1996. Introduction to quantitative genetics. 4th ed. Longman, Harlow, U.K.

Felsenstein, J. 1965. The effect of linkage on directional selection. Genetics 52:349–363.

Fenster, C. B., and L. F. Galloway 2000. The contribution of epistasis to the evolution of natural populations: a case study of an annual plant. Pp. 232–244 *in* J. B. Wolf, E. D. Broodie, and M. J. Wade eds. Epistasis and the evolutionary process. Oxford Univ. Press, Oxford, U.K.

Fierst, J. L., and T. F. Hansen. 2010. Genetic architecture and post-zygotic reproductive isolation: evolution of Bateson-Dobzhansky-Muller incompatibilities in a polygenic model. Evolution 64:675–693.

Fisher, R. A. 1918. The correlation between relatives on the supposition of Mendelian inheritance. Trans. R. Soc. Edinburgh 3:399–433.

Flatt, T. 2005. The evolutionary genetics of canalization. Quart. Rev. Biol. 80:287–316.

Flint, C., and T. F. C. Mackay. 2009. Genetic architecture of quantitative traits in mice, flies, and humans. Genome Res. 19:723–733.

Fuerst, C., J. W. James, J. Solkner, and A. Essl. 1997. Impact of dominance and epistasis on the genetic make-up of simulated populations under selection: a model development. J. Anim. Breed. Genet. 114:165–175.

Gavrilets, S. 1993. Equilibria in an epistatic viability model under arbitrary strength of selection. J. Math. Biol. 31:397–410.

Gavrilets, S. 2004. Fitness landscapes and the origin of species. Princeton Univ. Press, Princeton, NJ.

Gimelfarb, A. 1989. Genotypic variation for a quantitative character maintained under stabilizing selection without mutations: epistasis. Genetics 123:217–227.

Gjuvesland, A. B., J. O. Vik, J. A. Wooliams, and S. W. Omholt. 2011. Order-preserving principles underlying genotype-phenotype maps ensure high additive proportions of genetic variance. J. Evol. Biol. 24:2269–2279.

Griffing, B. 1960. Theoretical consequences of truncation selection based on the individual phenotype. Aust. J. Biol. Sci. 13:307–343.

———. 1961. Accommodation of gene-chromosome configuration effects in quantitative inheritance and selection theory. Aust. J. Biol. Sci. 14:402–414.

Goodnight, C. 1987. On the effect of founder events on the epistatic genetic variance. Evolution 41:80–91.

———. 1988. Epistasis and the effect of founder events on the additive genetic variance. Evolution 42:441–454.

Haag, E. S. 2007. Compensatory vs. pseudocompensatory evolution in molecular and developmental interactions. Genetica 129:45–55.

Hallander, J., and P. Waldmann. 2007. The effect of non-additive genetic interactions on selection in multi-locus genetic models. Heredity 98:349–359.

Hansen, T. F. 2006. The evolution of genetic architecture. Annu. Rev. Ecol. Evol. Syst. 37:123–157.

———. 2011. Epigenetics: adaptation or contingency? Pp. 357–376 *in* B. Hallgrimsson, and B. K. Hall eds. Epigenetics: linking genotype and

phenotype in development and evolution. University of California Press, Berkeley, CA.

Hansen, T. F., and G. P. Wagner. 2001a. Modeling genetic architecture: a multilinear theory of gene interaction. Theor. Popul. Biol. 59:61–86.

———. 2001b. Epistasis and the mutation load: a measurement-theoretical approach. Genetics 158:477–485.

Hansen, T. F., C. Pélabon, and D. Houle. 2011. Heritability is not evolvability. Evol. Biol. 38:258–277.

Hansen, T. F., J. M. Álvarez-Castro, A. J. R. Carter, J. Hermisson, and G. P. Wagner. 2006. Evolution of genetic architecture under directional selection. Evolution 60:1523–1536.

Hermisson, J., T. F. Hansen, and G. P. Wagner. 2003 Epistasis in polygenic traits and the evolution of genetic architecture under stabilizing selection. Am. Nat. 161:708–734.

Hill, W. G., M. E. Goddard, and P. M. Visscher. 2008. Data and theory point to mainly additive genetic variance for complex traits. PLoS Genet. 4:e100008:1–10.

Houle, D., C. Pélabon, G. P. Wagner, and T. F. Hansen. 2011. Measurement and meaning in biology. Quart. Rev. Biol. 86:3–34.

Huang, W., S. Richards, M. A. Carbone, D. Zhu, R. R. H. Anholt, J. F. Ayroles, L. Duncan, K. W. Jordan, F. Lawrence, M. M. Magwire, et al. 2013. Epistasis dominates the genetic architecture of *Drosophila* quantitative traits. Proc. Natl. Amer. Sci: *In press*.

Jannink, J.-L. 2003. Selection dynamics and limits under additive x additive epistastic gene action. Crop Sci. 43:489–497.

Jannink, J.-L., L. Moreau, G. Charmet, and A. Charcosset. 2009. Overview of QTL detection in plants and tests for synergistic epistatic interactions. Genetica 136:225–236.

Johnson, N. A. 2000. Gene interaction and the origins of species. Pp. 197–212 *in* J. B. Wolf, E. D. Broodie, and M. J. Wade eds. Epistasis and the evolutionary process. Oxford Univ. Press, Oxford, U.K.

Karlin, S. 1975. General two-locus selection models: some objectives, results, and interpretations. Theor. Pop. Biol. 7:364–398.

Kauffman, S. A. 1993. The origins of order. Self-organization and selection in evolution. Oxford Univ. Press, Oxford, U.K.

Kawecki, T. J. 2000. The evolution of genetic canalization under fluctuating selection. Evolution 54:1–12.

Keightley, P. D. 1996. Metabolic models in selection response. J. Theor. Biol. 182:311–316.

Kelly, J. K. 2005. Epistasis in monkey flowers. Genetics 171:1917–1931.

Kempthorne, O. 1954. The correlation between relatives in a random mating population. Proc. R. Soc. Lond. B 143:103–113.

Kimura, M. 1956. A model of a genetic system which leads to closer linkage by natural selection. Evolution 10:278–287.

———. 1965. Attainment of quasi linkage equilibrium when gene frequencies are changing by natural selection. Genetics 52:875–890.

Kimura, M., and T. Maruyama. 1966. The mutational load with epistatic gene interactions in fitness. Genetics 54:1337–1351.

Kondrashov, A. S. 1988. Deleterious mutations and the evolution of sexual reproduction. Nature 336:435–440.

Le Rouzic, A., J. M. Álvarez-Castro, and Ö. Carlborg. 2008. Dissection of the genetic architecture of body weight in chicken reveals the impact of epistasis on domestication traits. Genetics 179:1591–1599.

Le Rouzic, A., D. Houle, and T. F. Hansen. 2011. A modeling framework for the analysis of artificial-selection time series. Genet. Res. 93: 155–173.

Le Rouzic, A., J. M. Álvarez-Castro, and T. F. Hansen. 2013. The evolution of canalization and evolvability in stable and fluctuating environments. Evol. Biol. 40:317–340.

Lewontin, R. C. 1974. The genetic basis of evolutionary change. Columbia, NY.

Lewontin, R. C., and K. Koijma. 1960. The evolutionary dynamics of complex polymorphisms. Evolution 14:458–472.

Lynch, M., and B. Walsh. 1998. Genetics and analysis of quantitative characters. Sinauer, Sunderland, MA.

Lynch, M., J. Conery, and R. Bürger. 1995. Mutational meltdowns in sexual populations. Evolution 49:1067–1080.

Malmberg, R. L., and R. Mauricio. 2005. QTL-based evidence for the role of epistasis in evolution. Genet. Res. 86:89–95.

Maynard Smith, J. 1978. The evolution of sex. Cambridge Univ. Press, Cambridge, U.K.

Moore, J. H., and S. M. Williams. 2005. Biological vs. statistical epistasis. BioEssays 12:637–646.

Moreno, G. 1994. Genetic architecture, genetic behavior, and character evolution. Ann. Rev. Ecol. Syst. 25:31–45.

Mueller, J. P., and J. W. James. 1983. Effect of linkage disequilibrium of selection for a quantitative character with epistasis. Theor. Appl. Genet. 65:25–30.

Nagylaki, T. 1992. Introduction to theoretical population genetics. Springer, Berlin, Germany.

———. 1993. The evolution of multilocus systems under weak selection. Genetics 134:627–47.

Orr, H. A. 1995. The population genetics of speciation: the evolution of hybrid incompatibilities. Genetics 139:1805–1813.

Orr, H. A., and M. Turelli. 2001. The evolution of postzygotic isolation: accumulating Dobzhansky-Muller incompatibilities. Evolution 55:1085–1094.

Otto, S. P., and N. H. Barton. 2001. Selection for recombination in small populations. Evolution 55:1921–1931.

Pavlicev, M., A. Le Rouzic, J. M. Cheverud, G. P. Wagner, and T. F. Hansen. 2010. Directionality of epistasis in a murine intercross population. Genetics 185:1489–1505.

Pavlicev, M., E. A. Norgard, G. I. Fawcett, and J. M. Cheverud. 2011. Evolution of pleiotropy: epistatic interaction pattern supports a mechanistic model underlying variation in genotype-phenotype map. J. Exp. Zool. (Mol. Dev. Evol.) 316B:371–385.

Phillips, P. C. 2008. Epistasis—the essential role of gene interactions in the structure and evolution of genetic systems. Nat. Rev. Genet. 9:855–867.

Rice, S. H. 1998. The evolution of canalization and the breaking of von Baer's laws: modeling the evolution of development with epistasis. Evolution 52:647–656.

———. 2002 A general population genetic theory for the evolution of developmental interactions. Proc. Natl. Amer. Sci. 99:15518–15523.

———. 2004. Developmental associations between traits: covariance and beyond. Genetics 166:513–526.

Rieseberg, L. H., M. A. Archer, and R. K. Wayne. 1999. Transgressive segregation, adaptation and speciation. Heredity 83:363–372.

Rockman, M. V. 2012. The QTN program and the alleles that matter for evolution: all that's gold does not glitter. Evolution 66:1–17.

Roff, D. A. 1997. Evolutionary quantitative genetics. Chapman & Hall, New York, NY.

Shao, H. L. C. Burrage, D. S. Sinasac, A. E. Hill, S. R. Ernest, W. O'Brien, H. W. Courtland, K. J. Jepsen, A. Kirby, E. J. Kulbokas, et al. 2008. Genetic architecture of complex traits: large phenotypic effects and pervasive epistasis. PNAS 105:19910–19914.

Slatkin, M., and M. Kirkpatrick. 2012. Using known QTLs to detect directional epistatic interactions. Genet. Res. 94:39–48.

Templeton, A. R. 1981. Mechanisms of speciation—a population genetics approach. Ann. Rev. Ecol. Syst. 12:23–48.

———. 2000. Epistasis and complex traits. Pp. 41–57 *in* J. B. Wolf, E. D. Broodie, and M. J. Wade eds. Epistasis and the evolutionary process. Oxford Univ. Press, Oxford, U.K.

Turelli, M. 1984. Heritable genetic variation via mutation-selection balance: Lerch's Zeta meets the abdominal bristle. Theor. Popul. Biol. 25:138–193.

Turelli, M., and N. H. Barton. 1994. Genetic and statistical analyses of strong selection on polygenic traits: what, me normal? Genetics 138:913–941.

———. 2006. Will population bottlenecks and multilocus epistasis increase additive genetic variance? Evolution 60:1763–1776.

Ungerer, M. C., C. R. Linder, and L. H. Rieseberg. 2003. Effects of genetic background on response to selection in experimental populations of *Arabidopsis thaliana*. Genetics 163:277–286.

Wagner, A. 2005. Robustness and evolvability in living systems. Princeton Univ. Press, Princeton, NJ.

Wagner, G. P. 2010. The measurement theory of fitness. Evolution 64:1358–1376.

Wagner, G. P., G. Booth, and H. Bagheri-Chaichian. 1997. A population genetic theory of canalization. Evolution 51:329–347.

Wagner, G. P., M. D. Laubichler, and H. Bagheri-Chaichian. 1998. Genetic measurement theory of epistatic effects. Genetica 102/103:569–580.

Weinreich, D. M. 2005. The rank ordering of genotypic fitness values predicts genetic constraint on natural selection on landscapes lacking sign epistasis. Genetics 171:1397–1405.

Weinreich, D. M., R. A. Watson, and L. Chao. 2005. Perspective: sign epistasis and genetic constraint on evolutionary trajectories. Evolution 59:1165–1174.

Whitlock, M. C., P. C. Phillips, F. B.-G. Moore, and S. J. Tonsor. 1995. Multiple fitness peaks and epistasis. Ann. Rev. Ecol. Syst. 26:601–629.

Wolf, J. B., E. D. III Broodie, and M. J. Wade eds. 2000. Epistasis and the evolutionary process. Oxford Univ. Press, Oxford, U.K.

Wright, S. 1969. Evolution and the genetics of populations. Vol. 2: The theory of gene frequencies. Chicago Univ. Press, Chicago, IL.

———. 1977. Evolution and the genetics of populations. Vol. 3: Experimental results and evolutionary deductions. Chicago Univ. Press, Chicago, IL.

Young, S. S. Y. 1967. Computer simulation of directional selection in large populations II. The additive x additive and mixed model. Genetics 56:73–87.

Yukilevich, R., J. Lachance, F. Aoki, and J. R. True. 2008. Long-term adaptation of epistatic genetic networks. Evolution 62:2215–2235.

Zhivotovsky, L. A., and S. Gavrilets. 1992. Quantitative variability and multilocus polymorphism under epistatic selection. Theor. Popul. Biol. 42:254–283.

Zuk, O., E. Hechter, S. R. Sunyaev, and E. S. Lander. 2012. The mystery of missing heritability: Genetic interactions create phantom heritability. Proc. Natl. Amer. Sci. 109:1193–1198.

Zwarts, L., M. M. Magwire, M. A. Carbone, M. Verseteven, L. Herteleer, R. R. H. Anholt, P. Callaerts, and T. F. C. Mackay. 2011. Complex genetic architecture of *Drosophila* aggressive behavior. Proc. Natl. Amer. Sci. 108:17070–17075.

Associate Editor: I. Gordo

Appendix

DYNAMICS OF A TWO-LOCUS MODEL WITH EPISTASIS

As a simple illustration of the importance of epistasis in evolutionary dynamics, we can consider a genotype–phenotype map for two loci with two alleles each, as illustrated in Table A1. If we assume random mating, the dynamics of the model can be described by the four haplotype frequencies evaluated at the zygote stage. If we label the alleles at the two loci for A and a and B and b, the four haplotypes are ab, Ab, aB, and AB with frequencies p_1, p_2, p_3, p_4, respectively. According to Crow and Kimura (1970, p. 197; see also Kimura 1956, 1965), the dynamics of these can be described by the system of differential equations

$$dp_1/dt = p_1(m_1 - m) - rD,$$

$$dp_2/dt = p_2(m_2 - m) + rD,$$

$$dp_3/dt = p_3(m_3 - m) + rD,$$

$$dp_4/dt = p_4(m_4 - m) - rD,$$

where $D = p_1p_4 - p_2p_3$ is the coefficient of linkage disequilibrium, r is the rate of recombination incorporating any difference in reproductive rates between coupling and noncoupling haplotypes, the m_i are the Malthusian marginal fitnesses of the haplotypes and m is their population average. Because our purpose is merely to show by example that epistasis matters in evolutionary dynamics, we assume that the phenotypic trait is Malthusian fitness (i.e., we study linear directional selection). With the genotype–phenotype map in Table A1, the Malthusian marginal fitnesses are

$$m_1 = p_1 0 + p_2({}^{A}y) + p_3({}^{B}y) + p_4({}^{A}y + {}^{B}y + {}^{AB}E),$$

$$m_2 = p_1({}^{A}y + {}^{B}y + {}^{AB}E) + p_2(2{}^{A}y) + p_3({}^{A}y + {}^{B}y + {}^{AB}E) + p_4(2{}^{A}y + {}^{B}y + {}^{AAB}E),$$

$$m_3 = p_1({}^{B}y) + p_2({}^{A}y + {}^{B}y + {}^{AB}E) + p_3(2{}^{B}y) + p_4({}^{A}y + 2{}^{B}y + {}^{ABB}E),$$

$$m_4 = p_1({}^{A}y + {}^{B}y + {}^{AB}E) + p_2(2{}^{A}y + {}^{B}y + {}^{AAB}E) + p_3(2{}^{A}y + {}^{B}y + {}^{AAB}E) + p_4(2{}^{A}y + 2{}^{B}y + {}^{AABB}E),$$

$$m = p_1m_1 + p_2m_2 + p_3m_3 + p_4m_4,$$

where we have used the assumption of Hardy–Weinberg equilibrium as a result of random mating. In this set up, the parameters ${}^{x}E$ represent epistasis in the sense of deviation from additive interactions on an arithmetric scale. As discussed in Wagner (2010), Malthusian fitnesses are naturally additive and epistasis is hence properly measured as deviation from additivity on the arithmetric scale (for Wrightian fitness on a discrete generation-to-generation time scale epistasis is more correctly measured as deviation from multiplicative interactions). In this model the genotype ab/ab is

taken as reference genotype and ${}^{A}y$ and ${}^{B}y$ are the reference effects of substituting the A and B alleles into the reference genotype (see Hansen and Wagner 2001a). Assuming no dominance, the reference effects of substituting two A alleles or two B alleles are then $2^{A}y$ and $2^{B}y$, respectively. The parameter ${}^{AB}E$ describes epistatic deviance due to interaction between the substitution of one A allele and one B allele, the parameter ${}^{ABB}E$ describes the interaction between one A allele and two B alleles, etc.

In the multilinear framework, the epistasis is described with one parameter ε, which scales the effects of the substitutions as

$$ {}^{AB}E = \varepsilon {}^{A}y\, {}^{B}y, $$

$$ {}^{ABB}E = {}^{AAB}E = 2\varepsilon {}^{A}y\, {}^{B}y, $$

$$ {}^{AABB}E = 4\varepsilon {}^{A}y\, {}^{B}y. $$

Here a positive value of ε signify positive epistasis where substitutions increasing fitness will enhance the effects of further substitution, whereas a negative value of ε signify negative epistasis where substitutions increasing fitness will diminish or flip the effects of further substitutions. In the examples shown in Figure 1, the reference effects are set to ${}^{A}y = {}^{B}y = 1$, which are interpretable as Malthusian rates with units time^{-1}, and positive epistasis is modeled by $\varepsilon = 0.5$ and negative epistasis by $\varepsilon = -0.5$. On the chosen scale, $\varepsilon = 0.5$ means that the effect of the substitution b $\rightarrow$ B is enhanced with 50% if a substitution a $\rightarrow$ A has already happened, and an $\varepsilon = -0.5$ means that the effect of the substitution b $\rightarrow$ B is diminished with 50% if a substitution a $\rightarrow$ A has already happened (the units of ε are inverse of the trait units).

As shown in the figures of the main text, the dynamics of the model are dramatically altered by both the presence and type of epistasis. This has hardly anything to do with the dynamics of linkage disequilibrium. Altering the recombination rate r has little effect on the dynamics of haplotype frequencies or mean fitness unless r is very close to 0, and this is also true with weaker selection (not shown). Instead, the effects of epistasis comes about by changing the average effects of allele substitutions, and hence the additive genetic variance. The classical idea that evolutionary dynamics can be predicted by additive effects and additive variance holds true, but this example demonstrates that this does not imply that epistasis in the genotype–phenotype map is not dynamically important.

Table A1. The two-locus genotype–phenotype map.

	aa	Aa	AA
bb	0	${}^{A}y$	$2^{A}y$
Bb	${}^{B}y$	${}^{A}y + {}^{B}y + {}^{AB}E$	$2^{A}y + {}^{B}y + {}^{AAB}E$
BB	$2^{B}y$	${}^{A}y + 2^{B}y + {}^{ABB}E$	$2^{A}y + 2^{B}y + {}^{AABB}E$