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The role of epistatic gene interactions in the response to selection and the evolution of evolvability

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Abstract

It has been argued that the architecture of the genotype–phenotype map determines evolvability, but few studies have attempted to quantify these effects. In this article we use the multilinear epistatic model to study the effects of different forms of epistasis on the response to directional selection. We derive an analytical prediction for the change in the additive genetic variance, and use individual-based simulations to understand the dynamics of evolvability and the evolution of genetic architecture. This shows that the major determinant for the evolution of the additive variance, and thus the evolvability, is directional epistasis. Positive directional epistasis leads to an acceleration of evolvability, while negative directional epistasis leads to canalization. In contrast, pure non-directional epistasis has little effect on the response to selection. One consequence of this is that the classical epistatic variance components, which do not distinguish directional and non-directional effects, are useless as predictors of evolutionary dynamics. The build-up of linkage disequilibrium also has negligible effects. We argue that directional epistasis is likely to have major effects on evolutionary dynamics and should be the focus of empirical studies of epistasis.

Keywords: Epistasis; Gene interaction; Evolvability; Selection response; Genetic architecture

1. Introduction

Additive gene action is a crucial assumption of most models in evolutionary biology. Additive gene action means that the effect of an allele, or more precisely, of an allelic substitution, will be the same regardless of the genetic background in which it takes place. If in contrast, genes interact epistatically, the effect of an allelic substitution will necessarily depend on the genetic background. This has many ramifications, as a response to selection based on allele-frequency changes necessarily leads to a change in the genetic background of other genes, meaning that not just allele frequencies, but also allelic effects may change during a response to selection. This reasoning makes it clear that epistasis can alter additive genetic variances and covariances, and thereby affect the response to selection. When taken over many generations, such effects may be dramatic. The aim of this paper is to explore these effects in some detail and to assess their importance for evolutionary dynamics.

To proceed, it is helpful to make a distinction between statistical and functional/physiological epistasis (Cheverud and Routman, 1995; Hansen and Wagner, 2001a). Statistical epistasis refers to the standard quantitative genetic definition of epistasis as interaction terms in a regression of trait value on presence of alleles. Epistatic variance components, such as the additive-by-additive variance, V_{AA}, are the variances explained by the interaction terms in the regression. Statistical epistasis is a population property, and is a function of both allele frequencies and the biological interactions among genes. Functional epistasis, on the other hand, refers to non-additive interactions among loci in the mapping from specific genotypes to phenotype, and is not a population property. Cheverud and Routman (1995) used the term

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physiological epistasis to emphasize this distinction between physiological and statistical interactions. We use the term "functional" to emphasize that the genotype–phenotype map is not determined by physiology alone, but also by how traits interact functionally with each other and with the environment (e.g. in the case of most life-history traits).

Gene interaction has not been central in evolutionary quantitative genetics. This situation is certainly influenced by the fact that the definition of epistatic variance components in terms of residuals from the additive model minimize their effects (Whitlock et al., 1995; Phillips et al., 2000). Furthermore, the functional architecture (sensu Houle, 2001) of a trait will influence the trait's ability to respond to selection, but the epistatic variance components simply do not capture this influence. In particular, statistical epistasis does not describe directionality in the epistatic interactions, i.e. whether gene effects tend to reinforce or diminish each other along particular directions in morphospace.

Hansen and Wagner (2001a) argued that directional epistasis will affect the response to selection due to systematic changes in the effects of alleles as their genetic background changes. If the epistatic interactions are random and non-directional, these effects will tend to cancel out, but if there is a systematic directional pattern of gene interaction, then there will be a modified response to selection. Positive epistasis, where genes tend to reinforce each other's effects along the direction of selection, will accelerate the response, while negative epistasis, where genes tend to diminish each others effects in the direction of selection, will reduce the response. Over many generations, the dynamics of gene-effect reinforcement and competition can become very complex, and may lead to substantial departures from a simple additive response to selection.

It is well known that gene interactions may influence the additive genetic variance (e.g. Goodnight, 1987, 1988; Keightley, 1989; Cheverud and Routman, 1995; Hansen and Wagner, 2001a; Barton and Turelli, 2004). In particular, it has been argued that epistatic variance may be "converted" into additive variance by genetic drift when a population passes through a population bottleneck (e.g. Bryant et al., 1986; Goodnight, 1995; Cheverud and Routman, 1996; Cheverud et al., 1999; but see Lopez-Fanjul et al., 2002; Barton and Turelli, 2004). It is important to realize that this effect is not restricted to genetic drift. Changes in additive genetic variance occur because of changes in the genetic background, and any process that changes gene frequencies, including selection, will be able to change additive genetic variance in this manner (Hansen and Wagner 2001a).

Indeed, it has been shown that epistasis affects both mutational variability and the maintenance of genetic variance under stabilizing selection (e.g. Gimelfarb, 1989; Gavrilets, 1993; Gavrilets and de Jong, 1993; Wagner et al., 1997; Hermisson et al., 2003; Hermisson and Wagner, 2004), and several simulation studies with complex genotype–phenotype maps have shown that genetic architecture may change and that the evolution of evolvability can occur (e.g. Wagner and Altenberg, 1996; Porter and Johnson, 2002; Siegal and Bergman, 2002; Bergman and Siegal, 2003; Pepper, 2003). It has also been noted that epistasis has second-order effects on the response to directional selection (Nagylaki, 1992,1993; Turelli and Barton, 1994). These results are, however, not specific, and because they do not make a distinction between directional and non-directional epistasis, they do not provide insight in how epistasis may modify the response.

Gene interactions may also affect the response to selection through the buildup of linkage disequilibrium in association with favorable gene combinations. It is worth mentioning that it is not just (half) the additive effects that are transferred from parent to offspring, but also one fourth of the pairwise (A × A) epistatic effects and lesser fractions of higher-order interactions (Lynch and Walsh, 1998). This means that some of the linkage disequilibrium built by epistatic selection may be converted into a response to selection (Griffing, 1960). Linkage disequilibrium may also affect evolvability by generating hidden genetic variation under stabilizing selection (Lynch and Gabriel, 1983; Gavrilets and Hastings, 1995; Deng and Lynch, 1996), which may be released to power a selection response when the selective regime changes.

In this communication, we use analytical work and individual-based computer simulations to explore the role of gene interactions in the response to selection. The first goal is to demonstrate that epistatic interactions indeed have important effects on the evolvability of a quantitative trait. A second goal is to formulate and test hypotheses about what aspects of genetic architecture are important for determining the selection response. This will suggest statistics that may be useful in predicting the evolvability of a given population. We focus on the response to directional selection fueled by standing genetic variation. The long-term effects of new mutations will be explored elsewhere.

2. Model

2.1. The multilinear genotype–phenotype map

In general the genotype–phenotype map is an enormously complicated and largely unknown function, so some simplification is necessary to make a tractable model. Indeed, the additive model is a natural first approximation to the genotype–phenotype map, and its success reflects the fact that the additive effects are

essential parameters of evolution; but the additive effects are themselves evolvable entities, and the additive model cannot capture this second-order evolvability dynamics. The multilinear genotype–phenotype map, introduced by Hansen and Wagner (2001a), is an attempt at including evolvable additive effects by allowing gene effects (i.e. the effects of allelic substitution) to be linear functions of the gene effects at other loci, and thus multilinear functions of the entire genetic background. This is still a gross simplification of the genotype–phenotype map, but adds the essential features needed for studying the evolution of evolvability.

The multilinear model is sufficiently well behaved to allow many analytical results to be derived; see Hansen and Wagner (2001b) on the mutation load and the evolution of sex, and Hermisson et al. (2003) for more extensive results on the maintenance of variation and evolution of genetic architecture under a balance between mutation and stabilizing selection.

The multilinear model represents the genotype, g, of an individual as a set of reference effects: $g = \{{}^1y, \ldots, {}^ny\}$, where the reference effect, ${}^iy$, of a locus, i, is defined as the phenotypic effect of substituting the genotype at this locus into a designated reference genotype (which may differ in one or both of the alleles at this locus). If z is the genotypic value of the individual, the linearity assumption implies that the genotype–phenotype map takes the following form:

$$z = z_r + \sum_i {}^iy + (1/2!)\sum_i\sum_{j\neq i} {}^{ij}\varepsilon\, {}^iy\, {}^jy + (1/3!)\sum_i\sum_{j\neq i}\sum_{r\neq i,j} {}^{ijr}\varepsilon\, {}^iy\, {}^jy\, {}^ry + \ldots \quad (1)$$

where z_r is the genotypic value of the reference genotype, the ${}^{ij}\varepsilon$ and ${}^{ijr}\varepsilon$ are epistasis coefficients describing the interaction between loci given by the upper left indices, and summations are over all loci in g.

The reference effect of an allelic substitution is a special case of substituting the genotype of the whole locus. Let the reference effect of an allele k at locus i be given as ${}^{i(k)}a$, in such a way that the reference effect of a whole-locus genotype with alleles 1 and 2 is given as ${}^iy = {}^{i(1)}a + {}^{i(2)}a$. Dominance may be included, but will not be considered further in this paper.

The effect of an allelic substitution at a single locus in a background g is the product of the reference effect of that substitution and an epistasis factor,

$${}^{g\to i}f := 1 + \sum_{j\neq i} {}^{ij}\varepsilon\, {}^jy + (1/2!)\sum_{j\neq i}\sum_{r\neq i,j} {}^{ijr}\varepsilon\, {}^jy\, {}^ry + \ldots, \quad (2)$$

describing how the background g modifies the effect of a substitution on locus i relative to the reference genotype. Hence, a substitution at locus i with reference effect ${}^i\delta$ has effect ${}^{g\to i}f\, {}^i\delta$ if it takes place in the background of g. The upper-left index "$g\to i$" should be read as genotype g acting on locus i. The epistasis factor describing the change of an interaction among two loci i and j is denoted ${}^{g\to ij}f$, such that the effect of substitutions with reference effects ${}^i\delta$ and ${}^j\delta$ at these loci, which would have an epistatic effect equal to ${}^{ij}\varepsilon\, {}^i\delta\, {}^j\delta$ in the reference genotype, will instead have an epistatic effect equal to ${}^{g\to ij}f\, {}^{ij}\varepsilon\, {}^i\delta\, {}^j\delta$ in the background of g. Equations for ${}^{g\to ij}f$ and higher-order factors can be found in Hansen and Wagner (2001a).

By definition, epistasis means that the phenotypic effects of gene substitutions depend on the genetic background in which they take place. The parameters in the model will thus depend on the choice of reference genotype, and it is necessary to explicitly incorporate the "reference" genotype in which effects are measured into our model. General results may then be derived by use of a set of equations relating parameters measured in one reference to those measured in another. The relationship between parameters measured with reference to two different genotypes, g and h, are

$${}^iy_g = {}^{g\to i}f_h({}^iy_h - {}^id_h), \qquad {}^{ij}\varepsilon_g = \frac{{}^{g\to ij}f_h\, {}^{ij}\varepsilon_h}{{}^{g\to i}f_h\, {}^{g\to j}f_h}, \quad (3)$$

where the subscripts g and h refer to measurement with reference to genotype g and h, respectively (Hansen and Wagner, 2001a). The parameter ${}^id$ is the reference effect of the change at locus i from genotype h to g.

2.2. Quantitative genetics of the multilinear genotype–phenotype map

In this section we relate the parameters of the multilinear model to the statistical parameters in the standard quantitative genetics model. We begin by assuming Hardy–Weinberg and linkage equilibrium where rather simple relationships exist. Formal statements and proofs of the following relationships can be found in results 4.1 and 4.2 in Hansen and Wagner (2001a). The average excess (equal to the additive effect under linkage equilibrium) of an allele r at locus i is given as

$${}^{i(r)}\alpha := <z|\,{}^{i(r)}a> - <z> = <{}^{g\to i}f\, {}^iy|\,{}^{i(r)}a> - <{}^{g\to i}f\, {}^iy>, \quad (4)$$

where $<x|y>$ denotes the conditional expectation of x on y. We will also use a bar to denote expectation of simple variables (i.e. $\bar{x} = <x>$). If alleles are independent this reduces to

$${}^{i(r)}\alpha = {}^{\bar{g}\to i}f({}^{i(r)}a - <{}^{i(r)}a>), \quad (5)$$

where ${}^{\bar{g}\to i}f$ is the epistasis factor describing the action of the population mean genotype (i.e. $\bar{g} = \{{}^1\bar{y}, \ldots, {}^n\bar{y}\}$). If ${}^iV_a$ is the variance of the reference effects of alleles at locus i, the additive genetic variance of alleles is

${}^{i}V_{\mathrm{A}} = ({}^{\bar{g}\to i}f)^2\,{}^{i}V_a$, and the total additive variance is

$$V_{\mathrm{A}} = 2\sum_i ({}^{\bar{g}\to i}f)^2\,{}^{i}V_a, \tag{6}$$

The additive-by-additive genetic variance is

$$V_{\mathrm{AA}} = 2\sum\nolimits_i \sum\nolimits_{j\neq i} {}^{ij}\varepsilon^2\,{}^{\bar{g}\to ij}f^2\,{}^{i}V_a\,{}^{j}V_a = \theta^2 V_{\mathrm{A}}^2/2, \tag{7}$$

where θ^2, defined by this relation, cf. Eq. (12) below, is a measure of the variance-weighted average strength of functional epistasis. Thus, with multilinear epistasis the A × A-variance scales approximately with the square of the additive genetic variance.

2.3. Composite parameters describing epistasis

The numbers of genes and gene interactions affecting quantitative characters are so large that any meaningful conceptual description must be based on general system features and not on specific descriptions. Quantitative genetics handles this by the use of composite parameters, which capture the important features of the system. Examples of such composite parameters are additive effects, additive genetic variance, and the effective number of loci. Unfortunately, the composite parameters that have been used to describe gene interactions, notably the A × A-epistatic variance, have not been very useful, as they fail to capture many essential features, and particularly so in relation to selection dynamics. We will use a set of composite epistasis coefficients to describe the strength and directionality of functional epistasis. We start with coefficients describing the degree of directional epistasis acting on individual loci.

$${}^{i}\varepsilon := 2\sum\nolimits_{j\neq i} {}^{ij}\varepsilon_0\,{}^{j}V_{\mathrm{A}}/V_{\mathrm{A}}, \tag{8}$$

$${}^{i}\tau := 4\sum\nolimits_{j\neq i}\sum\nolimits_{r\neq i,j} {}^{ijr}\varepsilon_0\,{}^{j}V_{\mathrm{A}}\,{}^{r}V_{\mathrm{A}}/V_{\mathrm{A}}^2, \tag{9}$$

where ${}^{i}\varepsilon$ is a measure of pairwise directional epistasis acting on locus i, and ${}^{i}\tau$ is a measure of third-order directional epistasis acting on locus i. The subscript 0 means that the epistasis coefficients are measured with reference to a genotype with reference effect at every locus at the population mean. This choice of reference provides the simplest and most transparent equations. Positive values of these parameters mean that positive genetic changes tend to increase the effect of a change at locus i, while negative genetic changes decrease the effect of a change at locus i. Negative values of the epistasis coefficients have the opposite effect. If we take the variance-weighted average of these locus-specific coefficients over all loci we get composite directional epistasis coefficients for the entire system

$$\varepsilon := 2\sum\nolimits_i {}^{i}\varepsilon\,{}^{i}V_{\mathrm{A}}/V_{\mathrm{A}} = 4\sum\nolimits_i\sum\nolimits_{j\neq i} {}^{ij}\varepsilon_0\,{}^{i}V_{\mathrm{A}}\,{}^{j}V_{\mathrm{A}}/V_{\mathrm{A}}^2 \tag{10}$$

$$\tau := 2\sum\nolimits_i {}^{i}\tau\,{}^{i}V_{\mathrm{A}}/V_{\mathrm{A}} = 8\sum\nolimits_i\sum\nolimits_{j\neq i}\sum\nolimits_{r\neq i,j} {}^{ijr}\varepsilon_0\,{}^{i}V_{\mathrm{A}}\,{}^{j}V_{\mathrm{A}}\,{}^{r}V_{\mathrm{A}}/V_{\mathrm{A}}^3. \tag{11}$$

These parameters describe the overall directionality of epistasis, and will be small if both positive and negative interactions are common and cancel each other out. We also need parameters to measure the strength of non-directional epistasis. For pairwise interactions, there are two such parameters of importance.

$$\theta^2 := 4\sum\nolimits_i\sum\nolimits_{j\neq i} {}^{ij}\varepsilon_0^2\;\;{}^{i}V_{\mathrm{A}}\,{}^{j}V_{\mathrm{A}}/V_{\mathrm{A}}^2, \tag{12}$$

$$\omega^2 := 2\sum\nolimits_i {}^{i}\varepsilon^2\,{}^{i}V_{\mathrm{A}}/V_{\mathrm{A}} = 8\sum\nolimits_i\sum\nolimits_{j\neq i}\sum\nolimits_{r\neq i} {}^{ij}\varepsilon_0\,{}^{ir}\varepsilon_0\,{}^{i}V_{\mathrm{A}}\,{}^{j}V_{\mathrm{A}}\,{}^{r}V_{\mathrm{A}}/V_{\mathrm{A}}^3. \tag{13}$$

The θ^2 is a variance-weighted average of the squared epistasis coefficients, and is a measure of the overall strength of epistasis without regard to directionality. It is closely related to the A × A-epistatic variance as $\theta^2 = 2V_{\mathrm{AA}}/V_{\mathrm{A}}^2$. The ω^2 is a measure of the strength of the directional epistasis acting on individual loci, but differs from ε by not taking overall directionality into account. Thus ω^2 may be large even if individual loci are not modified in the same direction.

3. Analytical results

3.1. Response to linear selection

Hansen and Wagner (2001a) derived the following epistatic generalization of the Lande (1976, 1979) equation

$$\Delta\bar{z} = \beta V_{\mathrm{A}} + \frac{\varepsilon(\beta V_{\mathrm{A}})^2}{2} + \frac{\tau(\beta V_{\mathrm{A}})^3}{6} + \cdots, \tag{14}$$

where β is the selection gradient. See Appendix A for details. Note that only directional epistasis will modify the additive response. Positive epistasis in the direction of selection will increase the response, while negative epistasis will decrease the response. The effect of mth order epistasis on the response is proportional to the mth power of βV_{A}.

In Appendix A we derive an equation for the change in the additive genetic variance under selection assuming linkage equilibrium. This change has two (interacting) components. The first is due to changes in the allelic variances of individual loci, and the other is due to epistasis. If we only include terms that are first and second-order in the selection gradient, the change in the additive genetic variance is

$$\Delta V_{\mathrm{A}} = 2\beta\varepsilon V_{\mathrm{A}}^2 + \beta^2(\tau+\omega^2)V_{\mathrm{A}}^3 + 2\beta\sum\nolimits_i {}^{i}C_3 - 2\beta^2\sum\nolimits_i {}^{i}V_{\mathrm{a}}^2 + 4\beta^2 V_{\mathrm{A}}\sum\nolimits_i {}^{i}\varepsilon\,{}^{i}C_3 + \mathrm{o}(\beta^2), \tag{15}$$

where ${}^{i}C_3$ is the third cumulant of allelic reference effects at locus i, and ${}^{i}V_a$ is the variance in allelic reference effects at locus i. All parameters are measured with reference to a genotype where the allelic effects at all loci are set to their population mean.

The first two terms in this equation gives the change due to epistasis alone. The first term shows that directional pairwise epistasis (ε) is the only epistatic effect that is first-order in the selection gradient. Additive genetic variance will be increased by positive epistasis and decreased by negative epistasis. The epistatic effect scales with the square of the additive variance. The second term is due to directional third-order epistasis (τ), and locus-directional epistasis (ω^2). The ω^2-epistasis is different from overall directional epistasis in that it may be large even if the background acts differently on different loci, as long as each individual locus is modified in a consistent direction. The ω^2-epistasis is always positive, and will increase V_A regardless of the direction of selection. Non-directional epistasis, which enters only through θ^2, does not affect the response in either the mean nor in the variance.

The third and fourth terms are shared with the additive model (Barton and Turelli, 1987; Turelli and Barton, 1990; Bürger, 2000). The third term shows that systematic skew in the allelic distributions will make the additive variance evolve in the direction of the skew. This effect is first order in the selection gradient, and may be large if loci tend to develop skew in the same direction. The fourth term is the only one that applies to an additive model with symmetric allelic distributions. It shows that additive variance will decrease at a rate proportional to the square of the selection gradient and the square of individual allelic variances. This is a slow process for loci with small effects. The fifth term is due to an interaction between epistasis and skew in the allelic-effect distribution.

In Appendix B we study the multi-generation response of the mean and additive variance under weak selection, and show that this is affected by additional composite averages of directional epistasis weighted by higher-order cumulants of the allele distribution. These effects of higher cumulants are proportional to decreasing powers of the selection gradient, and also vanish when the allelic effects are normally distributed. We present a formal proof that any epistatic effect on the multigeneration response will be proportional to these measures of directional epistasis. This implies that the deterministic dynamics will be identical to that of the additive model in the absence of directional epistasis in this generalized sense even if $V_{AA}>0$.

3.2. Evaluating the size of the epistatic effect

To evaluate the epistatic contribution to the selection response, it is helpful to consider scale-free measures of the epistatic effects. The units of the pairwise epistasis coefficients are the inverse of the unit of the trait. For traits measured on a ratio scale, this suggests multiplying the pairwise epistasis coefficient with the trait mean to obtain a dimensionless epistasis parameter: ${}^{ij}\varepsilon_\mu = {}^{ij}\varepsilon\bar{z}$. A standardized epistasis coefficient with the value ${}^{ij}\varepsilon_\mu = 1$ means that a gene substitution with an effect on the phenotype equal to 10% of the trait mean will increase the effects of gene substitutions on the interacting locus with 10%. A gene substitution with a 1% effect will increase the effects of substitutions at the other locus by 1%, and so on. This standardization carries over to the composite epistasis coefficients such that $\varepsilon_\mu = \varepsilon\bar{z}$. Alternatively, we may standardize the epistasis coefficients with the standard deviation, σ, of the trait as ${}^{ij}\varepsilon_\sigma = {}^{ij}\varepsilon\sigma$.

We now examine the effect of ε_μ on the response in the trait mean. We ignore higher-order epistasis, and write the response as

$$\Delta\bar{z}_\mu = \frac{\Delta\bar{z}}{\bar{z}} = \beta_\mu I_A\left(1+\frac{\varepsilon_\mu\beta_\mu I_A}{2}\right), \tag{16}$$

where $I_A = V_A/\bar{z}^2$ is the mean-standardized additive variance, also known as the "evolvability", and $\beta_\mu = \beta\bar{z}$ is the mean-standardized selection gradient (Houle, 1992; Hansen et al., 2003; Hereford et al., 2004). Observe that $\beta_\mu I_A$ is the expected mean-standardized response of an additive model. Thus, the additive proportional response to selection is altered by a percentage approximately equal to $\varepsilon_\mu/2$ times the percentage response in the mean under an additive model. For example, if the expected additive response is 10% of the trait mean ($\beta_\mu I_A = 0.1$), and $\varepsilon_\mu = 1$, then the response will be about 5% larger than the additive prediction. If the expected additive response is 1% of the mean, and $\varepsilon_\mu\beta_\mu I_A = -0.5$, then the response will be reduced with 0.25% of its value. These numbers suggest that the direct epistatic effects on the response of the trait mean will usually be negligible. Episodes of directional selection capable of changing the trait mean by more than a few percent are presumably unusual in nature, and even then it seems that ε_μ need to be well in excess of 1 to have a significant effect on the mean response.

In contrast, we expect directional epistasis to be the main determinant of the selection response in the additive variance, and thus of the evolution of evolvability. On a mean-standardized scale, the first term of the response can be written

$$\Delta I_A = \frac{\Delta V_A}{\bar{z}^2} \approx 2\beta_\mu\varepsilon_\mu I_A^2. \tag{17}$$

We see that the proportional response in the evolvability will be approximately equal to $2\varepsilon_\mu$ times the proportional response in the mean under an additive model (i.e. $\beta_\mu I_A$). If $\varepsilon_\mu = 1$, and there is a 1% response in

the mean, the "evolvability" will increase with close to 2% per generation. It does not take many generations before this has accumulated into a dramatic change of evolvability.

4. Methods of simulation

Individual-based computer simulations were initialized first by the generation of an epistasis matrix representing the pairwise interactions between loci. A matrix of ${}^{ij}\varepsilon$ values was generated by drawing values from a normal distribution. The population consists of N individuals divided between two genders, the genders are identical and mating uses one individual from each gender. Each allele in each individual is initialized independently in the starting population. Alleles on the same locus are considered additive; for each individual the sum of the mean values of the two alleles at each locus defines the locus reference effect. The selection and mating steps were combined. To generate each offspring for the next generation, one parent of each gender was chosen, weighted by relative fitness, and one allele chosen randomly from each locus of each parent (taking account of recombination) and combined to construct the progeny. This is repeated N times to generate the next generation.

The fitness function we used was $W = 1 + \beta(z - \bar{z})$. This guarantees that the mean fitness stays at 1, and that the selection gradient w.r.t. relative fitness equals β regardless of $\bar{z}$.

All parameters and variables of the model were measured with reference to a hypothetical homozygous genotype with genotypic value equal to zero (i.e. the mean of the initial population if in linkage equilibrium). In doing comparisons between genetic architectures with different levels of epistasis, we kept the initial additive genetic variance constant at $V_A = 0.05$, which corresponds to a 5% unit change in additive trait under unit directional selection ($\beta = 1$). An equal amount of environmental variance was added to make the (narrow-sense) heritability equal to 0.5 in the additive case. Population sizes $N = 100$ and $N = 1000$, selection strengths $\beta = 0.1$ and $\beta = 1$, number of loci $n = 5$, 10 and 20 were explored. Simulations started with a population in Hardy–Weinberg and linkage equilibrium. If not otherwise mentioned, we assumed free recombination. Each simulation was repeated 100 times with the same parameter values, but different allelic reference effects were drawn each time. Results are represented as averages of these 100 trials. We deemed a population as having reached its selection limit, and stopped the simulation, when the variance of the sum of the allelic reference effects was less than 10^{-9}, which in practice means fixation on all loci.

We specified the distribution of the allelic reference effects, ${}^{i}a$, in the starting population by letting every allele be different with an effect drawn from a normal distribution with mean zero and variance ${}^{i}\sigma^2_y/2$, so that the variance of the reference effects at the locus was ${}^{i}\sigma^2_y$. We kept this variance the same at all loci, i.e. ${}^{i}\sigma^2_y = \sigma^2_y$, and set $\sigma^2_y = V_A/n$, which gives the correct additive genetic variance in the population when all alleles are independent and the mean reference effects of all loci are zero. We also tested non-normal allelic distributions with varying degrees of systematic skew and kurtosis.

Epistasis coefficients were drawn at random only on the level of the population, such that the epistasis coefficient describing the interaction among a particular set of loci is the same for all individuals in the population. Thus, epistasis coefficients are parameters and not variables of the simulation. In the standard simulation, the $n(n-1)$ pairwise epistasis coefficients were drawn at random from a normal distribution with specified mean and variance. We did not include higher-order epistasis in the simulations. In most of our simulations the epistasis coefficients had a mean of of -1, 0 or 1, and a standard deviation of 1. An epistasis coefficient of size 1 means that an allelic substitution with reference effect y will change the effect of subsequent substitutions with about y%. The mean starting reference effect in our standard simulation was about 0.03, which implies a 3% change in the mean effect of subsequent allelic substitutions at other loci. We also show some results with ${}^{ij}\varepsilon$ on the order of 0.1 implying a 0.3% change in the effect of interacting loci.

5. Simulation results

5.1. Response in relation to the functional architecture

Figs. 1 and 2 illustrate the responses in the trait mean and additive genetic variance to linear selection with different genetic architectures. These simulations are conducted with 20 freely recombining loci in a population of 1000 randomly mating individuals with selection strenght $\beta = 1$. Simulations with different numbers of loci, population sizes, selection strenghts, recombination rates, and allelic distributions, as specified in the methods, yield qualitatively similar results. The first thing to notice is that the responses are different for the different architectures. As predicted, strong positive directional epistasis leads to a rapid increase in the additive genetic variance associated with a faster response in the mean, and eventually a much higher selection limit is reached. Locus-directional epistasis has a similar, but less pronounced effect, while pure non-directional epistasis has a response that is essentially identical to that of an additive architecture. The slight differences that are observed may be due to some

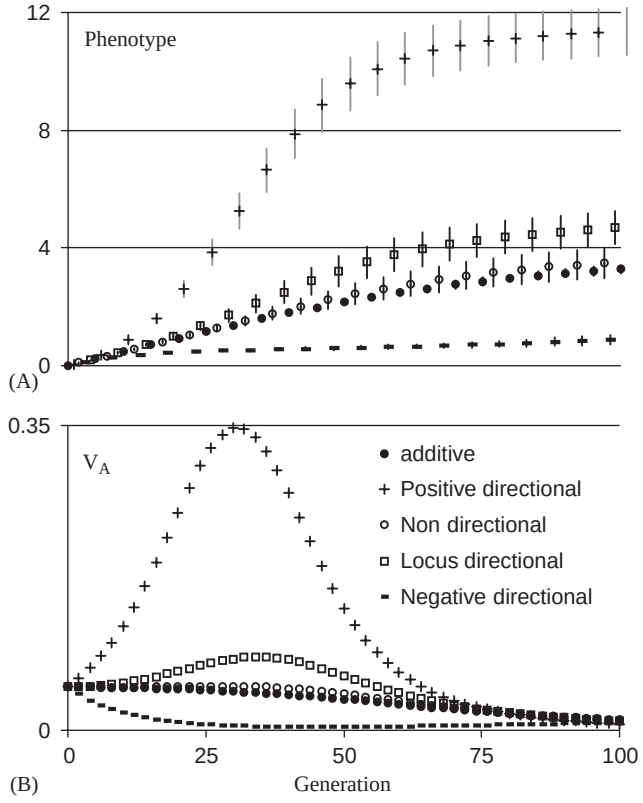

Fig. 1. Effects of epistasis on the response to selection. Plots of (A) trait mean and (B) additive genetic variance, V_A, are shown. The plots show the average over 100 trials (the bars in A are standard deviations over the 100 trials). For each trial $N = 1000$, $\beta = 1$, initial $V_A = 0.05$, initial heritability $= 0.5$. Five genetic architectures are depicted: positive epistasis (mean ${}^{ij}\varepsilon = 1$, SD$({}^{ij}\varepsilon) = 1$), locus-directional epistasis (mean ${}^{ij}\varepsilon = \pm 1$ in two non-overlapping modules, SD$({}^{ij}\varepsilon) = 1$ for all ${}^{ij}\varepsilon$), non-directional epistasis (mean ${}^{ij}\varepsilon = 0$, SD$({}^{ij}\varepsilon) = 1$), additive (${}^{ij}\varepsilon = 0$ for all ${}^{ij}\varepsilon$), negative epistasis (mean ${}^{ij}\varepsilon = -1$, SD$({}^{ij}\varepsilon) = 1$).

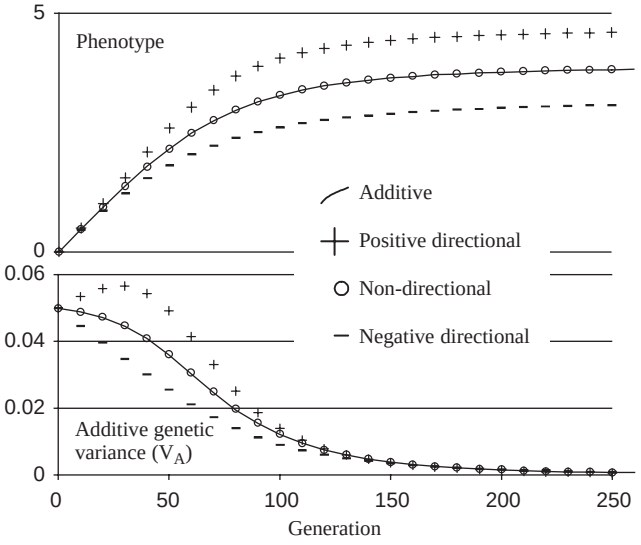

Fig. 2. Effects of weak epistasis. Plots of (A) trait mean and (B) additive genetic variance are shown. The mean values for selected generations from 100 trials are shown. Parameters as in Fig. 1 except that epistasis is much weaker. Four genetic architectures are depicted: positive epistasis (mean ${}^{ij}\varepsilon = 0.1$, SD$({}^{ij}\varepsilon) = 0.1$), non-directional epistasis (mean ${}^{ij}\varepsilon = 0$, SD$({}^{ij}\varepsilon) = 0.1$), additive (${}^{ij}\varepsilon = 0$ for all ${}^{ij}\varepsilon$), negative epistasis (mean ${}^{ij}\varepsilon = -0.1$, SD$({}^{ij}\varepsilon) = 0.1$). Locus-directional epistasis is not shown as it is indistinguishable from non-directional epistasis. An epistasis coefficient of 0.1 between two loci means that an average allele substitution on one locus will change the effects of substitutions at the other locus with about 0.3%.

random directional epistasis generated by random sampling of epistasis coefficients or by genetic drift. Thus, the theoretical prediction that the selection response is not affected by non-directional epistasis is valid for hundreds of generations until the selection limit is reached. This pattern appears robust to changes of parameters and initial conditions, except if the strength of epistasis is increased by orders of magnitude (see below).

As predicted, strong negative directional epistasis leads initially to a rapid reduction in additive genetic variance and an associated slow response in the mean (Fig. 3). Then, after reaching a plateau of very slow evolution, a second phase is reached where the additive genetic variance increases somewhat and a prolonged slow response is observed. This uptick is due to variation in epistatic effects, as it is not observed if all epistasis coefficients are identical (Fig. 3). In any event, the selection limits that are eventually reached are well below those of the additive case.

5.2. Effects of linkage disequilibrium

It has been suggested that the buildup of positive linkage disequilibrium could increase the response to selection. The simulations, however, show that the effects of linkage disequilibrium are insignificant. In Fig. 4, we show responses to selection with different degrees of linkage between loci, and also a case where alleles are scrambled each generation to remove all statistical dependencies among alleles both within and among loci. Note that there are practically no differences in the responses unless linkage is very tight. Only when average linkage falls below $r = 0.05$ is there a noticeable effect.

5.3. Strongly canalized genetic architectures

So far, we have discussed simulations were there is ample additive genetic variation present. We now turn to the dynamics of strongly canalized genetic architectures where additive variance is near absent, but where strong epistasis allows for a large amount of cryptic variation. We compared trials in which the additive effects of alleles were reduced by 10-fold (means and standard deviations of epistasis coefficients increased 100-fold to preserve the magnitude of the epistasis terms), and one hundredfold (means and standard

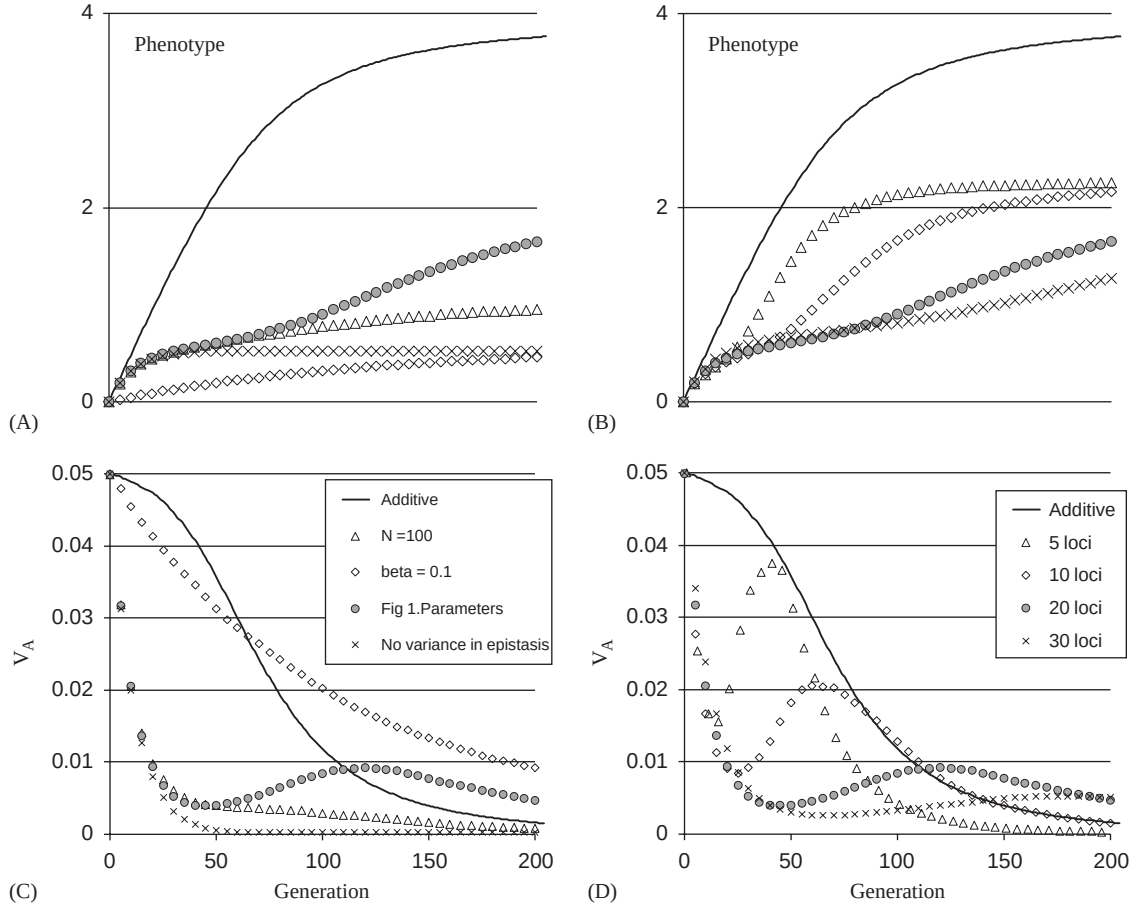

Fig. 3. Negative epistasis with different parameter values. Plots of (A,B) mean phenotypes and (C,D) additive genetic variance are shown. The mean values for each generation (from 100 trials) for the first 200 generations are shown. Parameters as Fig. 1 unless otherwise noted. Each figure shows an additive architecture with 20 loci (black line) and negative epistasis as in Fig. 1 (filled circles). (A) and (C) show the effects of weaker selection ($\beta = 0.1$, open diamonds), lack of variance in epistasis coefficients (all ${}^{ij}\varepsilon$ values equal, x symbols), and small population size ($N = 100$, open triangles). (B) and (D) show the effects of varying the number of loci by using 5 (open triangle), 10(open diamond), 20(filled circle), and 30 (x symbols) loci. In (B) and (D), allelic effects were adjusted to keep V_A the same, and epistasis coefficients adjusted to have the same average effect on subsequent substitutions. Note that variance in the epistasis coefficients is needed for the secondary increase in V_A.

deviations of epistasis coefficients increased by ten thousand-fold) relative to the above trials. Fig. 5 illustrates the characteristic dynamics of these cases. At first there is no response, but then after some 30–100 generations a response will start and rapidly pick up pace. Architectures with positive epistasis respond most quickly while negative directional and non-directional epistasis will take more time. Interestingly, even non-directional epistasis allows a response greatly exceeding the additive case. Pure negative epistasis without variation in epistasis, however, will not allow any response in these cases (not shown). The response in the runs with negative epistasis is entirely due to variation in epistasis, and thus appears identical to non-directional epistasis.

Although selection limits are smaller for these canalized architectures than for the non-canalized architectures studied above, they are of a similar order of magnitude. Altogether, we have demonstrated that a breakdown of canalization and a release of cryptic genetic variation can occur under directional selection.

5.4. Testing the theoretical predictions

The theoretical predictions for the response in the mean and variance are approximations, which ignore the effects of genetic drift, linkage, linkage disequilibrium, Hardy–Weinberg disequilibrium, and higher-order terms in the selection gradient. Our simulations do, however, show that the predictions from these equations are close to perfect for most of the circumstances we explored. This is illustrated in Fig. 6. Even with relatively strong linkage and selection, the theory predicts the selection response accurately over hundreds of generation until the selection limit is reached. Furthermore, if we decompose the prediction into

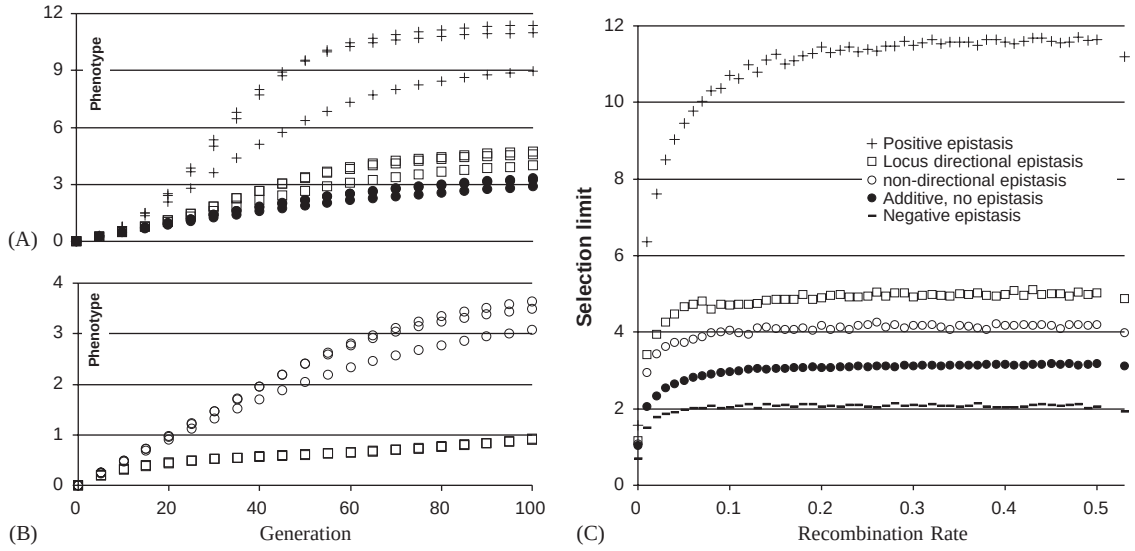

Fig. 4. The effects of linkage and magnitude of epistasis on the response to selection. (A,B) Plots of the response to selection for a series of populations with the same parameter values and genetic architectures as in Fig. 1, but with varying levels of recombination between adjacent loci. For each genetic architecture, responses with three levels of recombination are shown: $r = 0.5$, alleles scrambled each generation, and $r = 0.05$. Panel A shows positive epistasis, locus-directional epistasis, and additive architectures. Panel B shows non-directional and negative epistatic architectures. For each architecture free recombination shows the faster response, followed by scrambled alleles, and $r = 0.05$. (C) The selection limit (mean of generations 980–1000, well after fixation for almost all trials) for different degrees of recombination between adjacent loci (far right are the results of trials in which the alleles at each were randomly redistributed between each generation, eliminating any linkage disequilibrium).

separate terms, we see that the change in the variance is dominated by the first and the third term of Eq. (15), representing directional epistasis and the third cumulant of the allelic distributions, respectively. In other words, the change in the variance is well predicted by $\Delta V_A \approx 2\beta(\varepsilon V_A^2 + \sum_i {}^iC_3)$. The importance of the third cumulant of the allelic distribution also appears to be an indirect consequence of epistasis, as a strong negative skew tends to evolve in the presence of positive epistasis. In the additive case the skew is smaller, and the slow dynamics in this case are determined by the familiar combination of third cumulant and squared allelic variance (Bürger, 2000). We also note that the squared allelic variance may become more influential in genetic architectures dominated by a small number of loci.

In Fig. 7 we show some examples of starting with various non-normal allelic distributions. In all cases we explored, the predictions from Eq. (15) were very accurate, and the dynamics were dominated by directional epistasis and the third cumulant of the allelic distribution. This holds whether we start with positively or negatively skewed, or platykurtic or leptokurtic distributions. No qualitiative result seems dependent on Gaussian allelic distributions.

The predicted dynamic equivalence between additive and non-directional epistatic architectures appears very robust. The only exception occurs with strongly canalized architectures (Fig. 5), and may be partially due to some locus-directional epistasis generated by genetic drift, since epistasis is very strong in these simulations.

5.5. Evolution of genetic architecture

The composite epistasis parameters, ε, θ^2, and ω^2, do not stay constant during a response to selection, and changes in these parameters induce changes in the dynamics of the mean and variances. In Fig. 8 we show some examples of how these entities evolve. These, and numerous other simulations (not shown), reveal that large and rapid changes in genetic architecture typically take place. If we start out with relatively strong epistasis, the genetic architecture may be completely altered within a few dozen generations. Changes in the composite epistasis parameters are partially due to changes in the variances of different loci used as weights, but more importantly, they are due to changes in the effects of the genes themselves. The predictive equations are based on the assumption that all parameters are measured with reference to the population mean, so since the population mean is changing, the parameters will also change. Because the generation-to-generation dynamics depend on the parameters as measured in the current population (as represented by the mean reference), these changes may be considered as evolution of genetic architecture, and they are necessary to understand changes in long-term dynamics. The pattern shown in Fig. 8, which is quite robust, shows that epistasis coefficients tend to evolve to become more negative regardless of their starting conditions. Positive epistasis evolves towards zero, non-directional epistasis stays relatively stable, and negative epistasis evolves to become more negative. The evolution of the negative

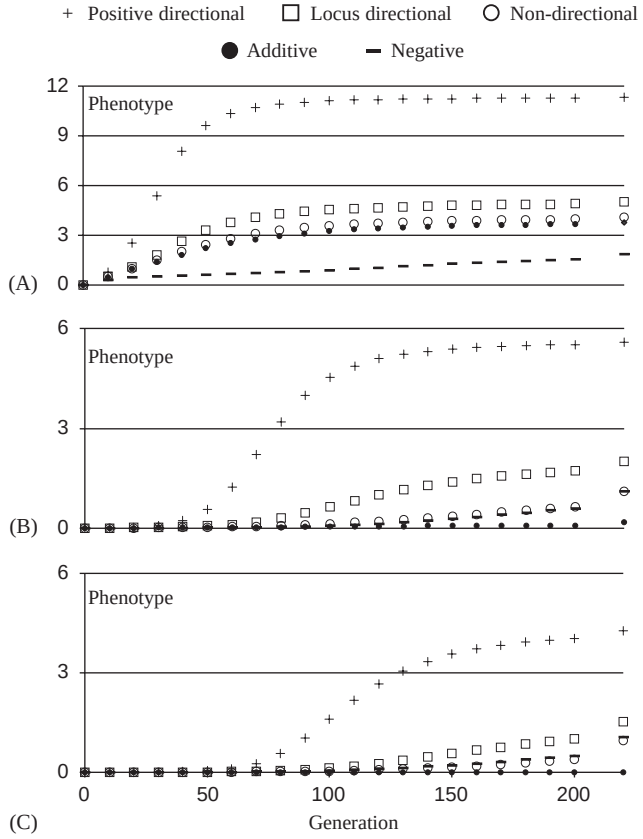

Fig. 5. Response with strongly canalized genetic architectures. The mean values for 200 generations and the selection limit from 100 trials are shown. For each trial $N = 1000$, $\beta = 1$, there is no environmental variance. (A) Parameters are as in Fig. 1; (B) additive effects of alleles are reduced by 10-fold (epistasis coefficient means and SD increased 100-fold); (C) additive effects reduced by 100-fold (epistasis coefficient means and SD increased 10000-fold). Note: (i) the delay in initiation of response with reduced additive effects; (ii) the final selection limit achieved for negative epistasis (exceeding first additive and then both additive and non-directional cases for strongly canalized architectures) and (iii) the non-linear relationship between reduction in additive effects and final selection limit achieved (i.e., 10- and 100-fold reductions in additive effects result in merely two and three-fold reductions in selection limit respectively).

epistasis eventually turn and evolves back towards zero. This may explain the uptick in the evolution of the mean and variance observed in Figs. 1 and 3. A detailed study of the evolution of epistatic effects will be reported in a separate publication.

6. Discussion

Our results demonstrate that epistasis may have a strong effect on the response to directional selection. This effect is mainly due to the evolution of evolvability that happens through the ability of directional epistasis to change the additive genetic variance. Positive directional epistasis generates an acceleration in the selection response and an elevated selection limit. Negative directional epistasis leads to canalization, and although a subsequent increase in evolvability may take place, the selection limits are still below those expected under an additive architecture. Pure non-directional epistasis has no significant effects on the response as long as some additive genetic variance is present. It does, however, allow for an eventual breakdown of canalization in architectures that are initially void of additive genetic variance. Contrary to expectation, we found that linkage and linkage disequilibrium have negligible effects on the response to linear selection even in the presence of relatively strong epistatic interactions.

Importantly, the measures of directional epistasis that affect the selection response do not coincide with the classic genetic interaction variance, or any of its components. Epistatic variance components do not distinguish between directional and non-directional forms of epistasis, and it is possible to increase any component of the interaction variance without altering directional epistasis and, therefore, without altering the selection response. In particular, if directional epistasis is absent, the selection response follows the predictions from the additive model, even if substantial epistatic variance is present. This shows that some, but not all of the genetic variation that is "stored" in the population as epistatic variance is used in the multi-generation selection response. The crucial quantity needed to predict the effect of epistasis on selection response and selection limits is not given by epistatic variance components, but by measures of directional epistasis.

These results raise the question of whether directional epistasis is likely to be a common feature of natural genetic systems. Despite the fact that epistatic effects have been estimated throughout the history of population genetics, there is relatively little empirical information on this question. Estimates of classical epistatic variance components are of little value here, as these do not distinguish between directional and non-directional forms of functional epistasis. Classical line-cross analysis, on the other hand, can be used to detect directional effects, but such analyses are usually done between two inbred lines, which may not be representative, or between members of distinct populations, which does not necessarily correspond to the directionality of effects within a population. Still, a reanalysis of line-cross experiments with an eye to estimating composite epistasis coefficients or epistasis factors may be a fruitful way of approaching the problem. Indeed, some studies from natural populations have found evidence of directional epistasis being involved in population differences (e.g. Bradshaw and Holzapfel, 2000).

More detailed estimates of functional epistatic effects may be obtained from QTL analysis. The overall impression from the the litterature is that epistasis among QTLs is largely non-directional (e.g. Weber et al., 1999;

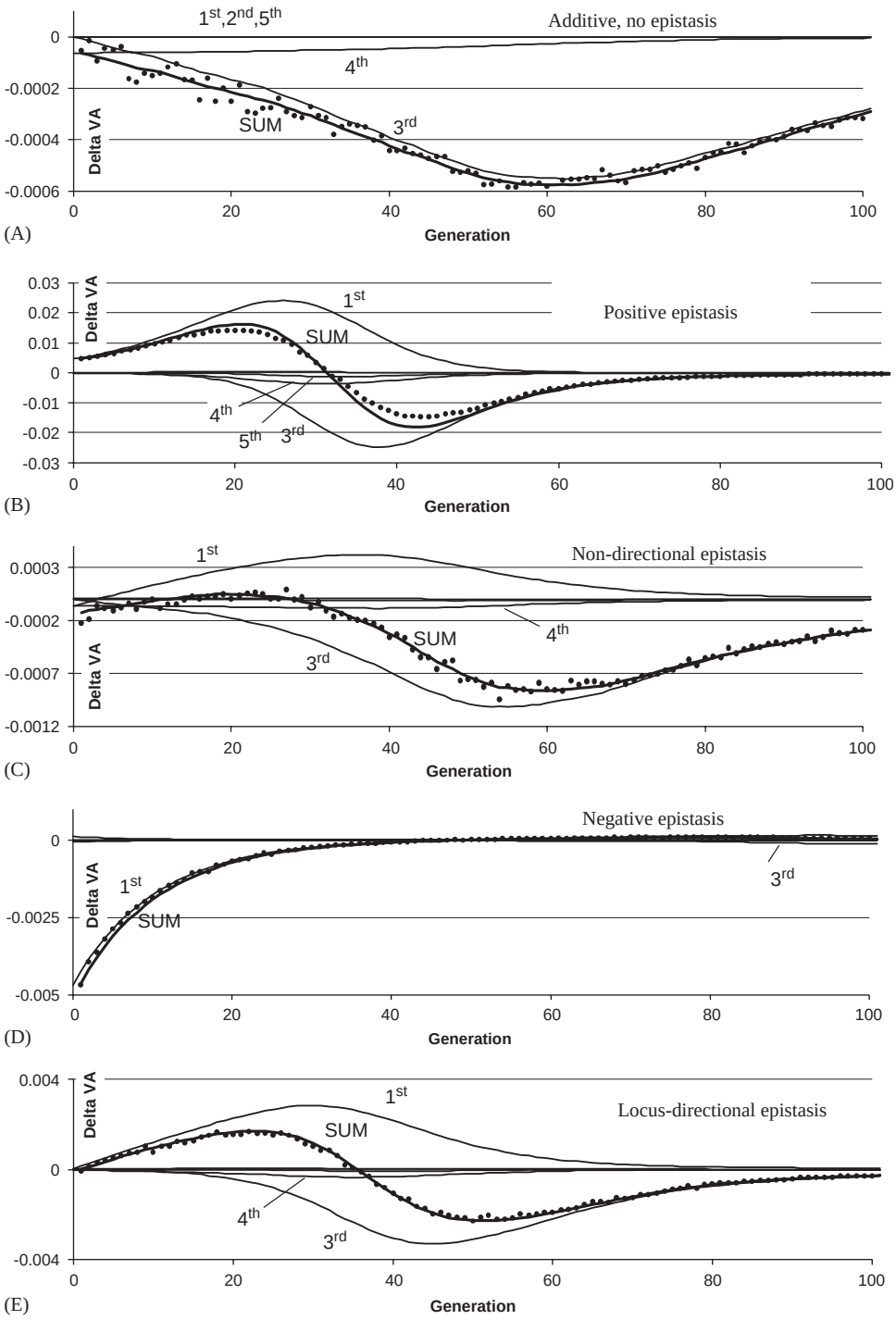

Fig. 6. Accuracy of analytical prediction for changes in the additive genetic variance (ΔV_A). On each plot the values of the first five terms in Eq. (15) and their sum are shown as well as the observed ΔV_A from simulations (points), the parameters and types of epistasis are the same as in Fig. 1. Terms not labeled are negligible. Note that the only important terms are the first (directional epistasis) and the third (third cumulant of allelic distribution).

2001; and see Fenster et al., 1997; Cheverud, 2001; Mackay, 2001 for general review). It should be remembered, however, that current methods of QTL analysis are severely biased toward detecting few interactions of large effect. This is due to the use of significance testing for individual effects, which leads to extremely low power when it comes to interaction effects. To get a reliable picture of epistasis among QTLs, we need careful studies specifically aimed at estimating average epistatic effects across all loci. This necessitates the development of statistical methods that avoids the pitfalls of significance testing.

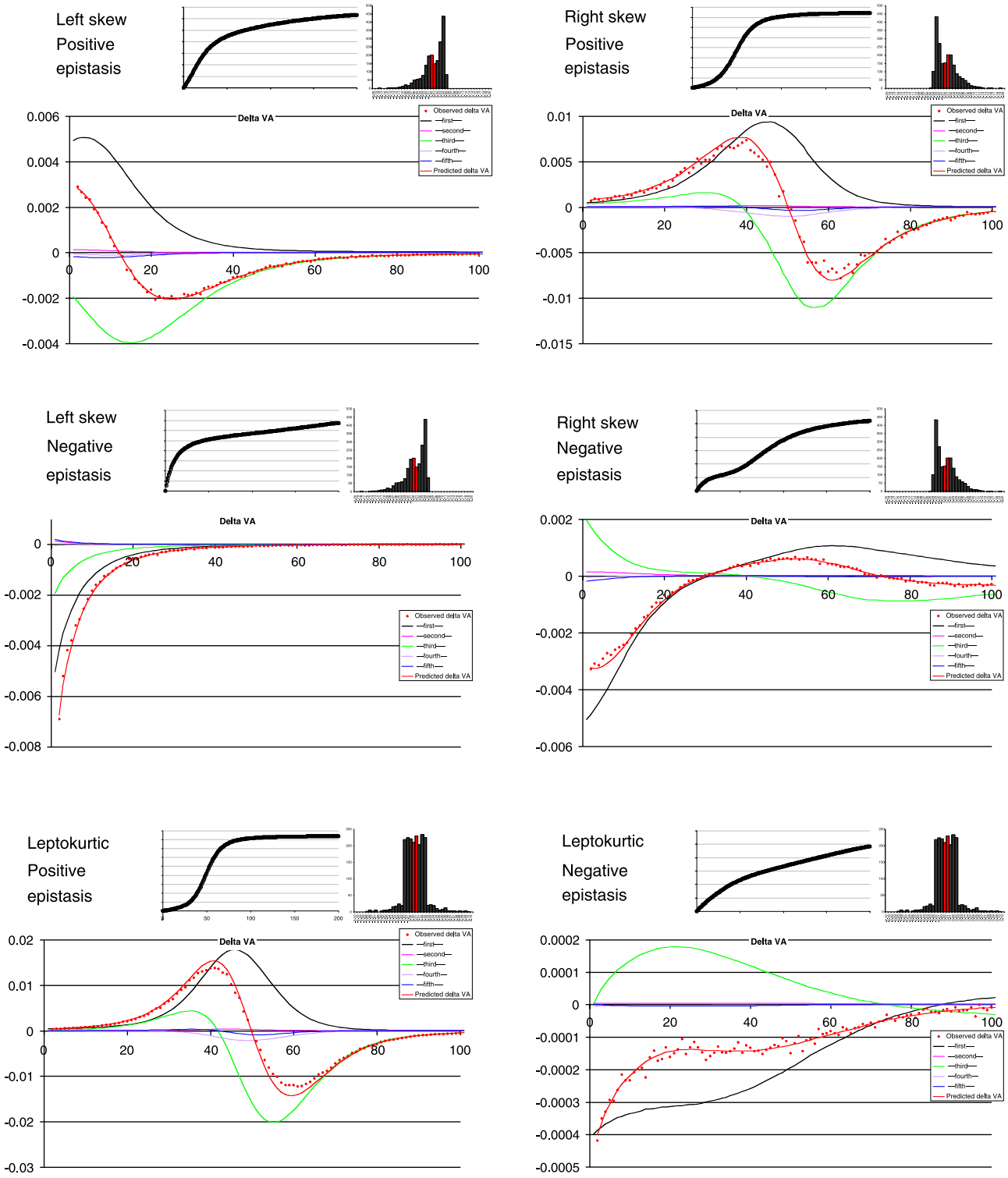

Fig. 7. Effects of directional epistasis with non-normal allelic distributions. Each plot shows the change in additive genetic variance (ΔV_A), as in Fig. 6, along with the response of the mean (upper-left inset) starting from a specified allelic distribution (upper-right inset). Averages over 50 trials are shown. The allelic variances were set to 0.05, except for the leptokurtic distributions and the left-skewed distribution with positive epistasis were the allelic variances were set to 0.015 to avoid many zero fitness values. Except for allelic distributions and no environmental variation, parameter values are the same as in Fig. 1. Note different scales on different figures.

Due to its potential importance for the maintenance of sexual reproduction (Kondrashov, 1988; Hansen and Wagner, 2001b), a number of studies have looked for evidence of synergistic epistasis among deleterious fitness mutations (Mukai, 1969; Clark and Wang, 1997; de Visser et al., 1997a, b; Elena and Lenski,

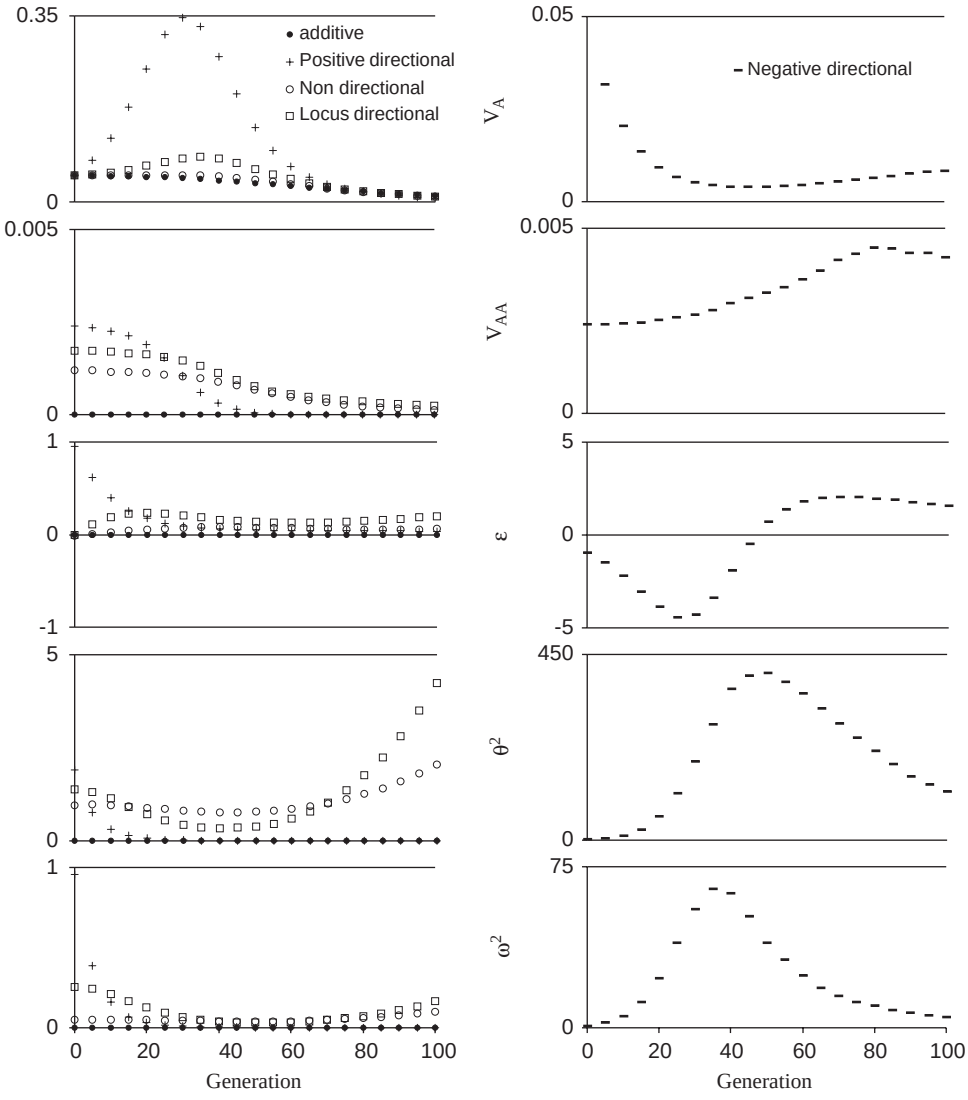

Fig. 8. The evolution of genetic architecture: Composite parameters describing the strength and type of epistasis are plotted against time with parameters as in Fig. 1. Left figures show the additive (filled circle), positive (plus sign), non-directional (open circle), and locus directional (open square) epistasis cases. Figures on the right represent negative epistasis (minus sign). Descending from the top are the additive genetic variance, additive-by-additive epistatic variance, ε, θ^2, and ω^2.

1997, 2001; Whitlock and Bourguet, 2000; Remold and Lenski, 2004). Synergistic epistasis means that deleterious mutations tend to increase the deleterious effects of each other. This would then correspond to negative epistasis in the direction of selection in our terminology. Although there are some indications of synergistic epistasis in these studies, the collective results appear conflicting and equivocal.

The pattern of response to artificial selection is also a useful source of information about genetic architecture. In general, the data seems broadly consistent with the additive model (e.g. Bürger, 1993; Zhang and Hill, 2005). For example, the increase in additive genetic variation predicted under strong positive directional selection is rarely observed in responses to artificial selection, and may taken as an indication that strong positive epistasis is not common. Selection responses typically decellerate after a varying number of generations. This is consistent with negative epistasis, but also with simple exhaustion of additive variance.

In the absence of a clear picture of the strength or frequency of directional epistasis in nature, we may ask whether directional gene interactions are to be expected on theoretical grounds. This question can be investigated in two ways; we can ask if there are aspects of organismal architecture that would tend to generate directional effects, and we can ask if particular directional effects may be the expected outcome of evolutionary dynamics.

The complexity of the genotype–phenotype map leads us to expect that epistatic interactions must be common (e.g. Wagner and Altenberg, 1996; Rice, 1998, 2000,

2002; Wolf et al., 2001). The complexity may, however, also lead us to expect a variety of different types of interactions that may tend to cancel in direction. Work on simple metabolic networks has revealed some predictable epistasis between perturbations at particular places in the network (Keightley, 1989; Szathmáry, 1993; Omholt et al., 2000), but there are reasons to be skeptical as to whether this can be extrapolated to complex phenotypic traits. After all, the development of most phenotypic traits involve a series of nonlinear mappings from a large number of gene regulatory and metabolic networks, and it is difficult to make general predictions about the pattern of functional gene interactions for complex traits. On the other hand, the variational properties of some traits may be dominated by a few modules that interact with each other as units. If so, genes affecting different modules may be expected to interact in a systematic manner. For example, if module A inhibits growth of module B, then all gene substitutions with positive effects on A will tend to interact negatively with all gene substitutions with positive effects on B. In such cases directional epistasis may appear.

Just as additive effects may evolve, epistatic effects may evolve. This may be caused by the presence of higher-order epistatic interactions, which by definition mean that lower-order epistasis terms are dependent on the genetic background. The directionality of the higher-order epistasis will then determine the direction of evolution of the lower-order terms. Epistasis coefficients may also evolve in the sense that they appear different when measured with reference to an evolving mean genotype. In operational terms, if we measured reference effects and epistasis coefficients with reference to the population mean before and after an episode of directional selection, we would obtain different readings. In a forthcoming article we explore this effect by studying changes in the measurements of epistasis coefficients with reference to the population mean. Our simulations, as well as analytical arguments, point to a general long-term tendency for epistasis coefficients to become more negative during directional selection. For traits under prolonged directional selection, we predict that positive interactions become weaker, leading to the evolution of an additive genetic architecture. Negative interactions, however, become stronger, such that the potential for canalization will increase. This may eventually lead to an epistatic constraint (sensu Hansen and Houle, 2004) on further evolution. We may thus contemplate the possibility that there exist traits that have been stopped in their evolutionary tracks by epistatic constraints built by prolonged directional selection. On the other hand, prolonged directional selection may not be the most realistic model of evolutionary change if traits, at least temporarily, reach local peaks in the adaptive landscape. Hermisson et al. (2003) studied the behavior of the multilinear model in a balance between mutation and stabilizing selection, and found that strong canalization may or may not evolve depending on parameter values. They also found that directional epistatic effects would evolve to become weak at equilibrium. This result depends on the assumption of unrestricted allelic reference effects, but may point to a general evolutionary tendency to weaken directional epistasis.

In any event, epistatic genetic architecture is instrumental in determining the speed and potential for adaptation to environmental change. It is thus unfortunate that the role of epistasis in adaptation has been largely ignored in the evolutionary quantitative genetics literature. The only effect that has been analyzed in depth is the possibility of "converting" epistatic variance to additive variance by genetic drift during population bottlenecks (see references in the Section 1). Our results make it clear that the interaction between selection and epistasis is usually going to be much more pronounced than any likely effect of drift. For example, in their study of the evolution of photoperiodism during the postglacial northward expansion of pitcher-plant mosquitoes (*Wyeomia smithii*), Bradshaw and Holzapfel (2000, 2001) found increased levels of additive genetic variance for photoperiodism and developmental time in the northern populations, and suggested that this may be due to "conversion" of epistatic variance by drift during colonization events. In the light of our results, an alternative explanation would be evolution of increased additive variance due to directional selection combined with positive epistasis. Indeed, the data, originally from Hard et al. (1992, 1993), presented in Bradshaw and Holzapfel's (2000) Fig. 15.6 A and C seem to indicate positive epistasis in direction of the northern phenotypes.

Multilinearity means that changes in the genetic background can only stretch or compress the relative effects of different genotypes at a locus. The order of genotypic effects on the trait can thus not be changed, except by the complete flipping of all effects that occur when epistasis factors become negative. This means that only additive effects, and not dominance relationships between alleles, can evolve under the multilinear model. Multilinearity does not exclude dominance, or even $A \times D$ and $D \times D$ effects, but the multilinearity constrains the dominance effects to evolve only in proportion to the additive effects (see Hansen and Wagner, 2001a for details). This means that dominance, as well as over- or under-dominance, can never evolve unless initially present. Clearly, the evolutionary dynamics may look quite different if there is potential for over-dominance to evolve. Results derived from the multilinear model are therefore strictly results about, or deriving from, the evolvability of additive effects. We choose to study the multilinear model because change in

additive effects is the most fundamental aspect of the evolution of evolvability, and because we believe that it is the most general model that allows general analytical results to be derived for multilocus systems. To study truly nonlinear forms of gene interaction, we have to turn to highly specific architectures, and rely almost exclusively on computer simulations.

Although evolutionary dynamics appear much more complex when gene interaction and the evolution of evolvability are taken into account, the dynamics of the additive genetic variance may in fact be easier to understand since it is dominated by directional epistasis. In the additive case, the additive variance appears relatively stable and the small changes we expect depends on practically unknowable genetic details such as the skew of the allelic distributions (Barton and Turelli, 1987). This again underscores the need for empirical estimates of directional epistasis.

Acknowledgments

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Appendix A. Response to selection in the trait mean and variance

If the trait is under linear directional selection with selection gradient β, and all alleles are independent of each other, then the change in the mean reference effect at locus i over one generation is

$$\Delta < {}^{i}y > = 2s\,{}^{i}V_a, \tag{A.1}$$

where $s = \beta < {}^{g\to i}f >$ is the selection coefficient and $2\,{}^{i}V_a$ is the additive genetic variance in the locus reference effect. The response to selection in the trait due to allele-frequency changes is thus (Hansen and Wagner, 2001a, Result 4.3):

$$\begin{aligned}\Delta\bar{z} = \beta V_A &+ (2\beta)^2 \sum_i \sum_{j>i} < {}^{g\to ij}f > {}^{ij}\varepsilon < {}^{g\to i}f > {}^{i}V_a < {}^{g\to j}f > {}^{j}V_a \\ &+ (2\beta)^3 \sum_i \sum_{j>i} \sum_{r>j} < {}^{g\to ijr}f > {}^{ijr}\varepsilon \\ &< {}^{g\to i}f > {}^{i}V_a < {}^{g\to j}f > {}^{j}V_a < {}^{g\to r}f > {}^{r}V_a + \cdots .\end{aligned} \tag{A.2}$$

Using the definitions from the main text, we can rewrite this as (14) in the main text.

Under linkage equilibrium the additive genetic variance is $V_{\mathrm{A}} = 2\sum_i {}^{i}V_a = 2\sum_i < {}^{g\to i}f > {}^{i}V_a^2$. Thus, changes in the additive genetic variance can result either from changes in the variance of the reference effects at individual loci, or from changes in the average epistasis factors that act on those loci. Changes in the variance of the reference effects depend on the allelic distribution at the locus according to the general formula for change in variance due to linear directional selection with slope s, as

$$\Delta\,{}^{i}V_a = s\,{}^{i}C_3 - s^2\,{}^{i}V_a^2, \tag{A.3}$$

where ${}^{i}C_3$ is the third cumulant of the allelic distribution at locus i. This can be derived by a straightforward application of the Price (1970) theorem. If the allelic variance is small or selection is weak, the dynamics of the reference effects are determined by the third cumulant of their distribution. Thus, the variance of the reference effects will remain approximately constant as long as this distribution is symmetrical (e.g. gaussian).

Changes in the mean epistasis factors acting on the loci constitute the other source of change in the additive genetic variance. The change in the mean epistasis factor is best expressed by measuring effects with reference to a genotype where the effect of each locus is at the population mean. Thus, the mean reference effects are all zero, and the average epistasis factor after selection can be expressed as

$$\begin{aligned}< {}^{g\to i}f >' = 1 &+ \sum\nolimits_{j\neq i} {}^{ij}\varepsilon_0 \Delta < {}^{j}y > \\ &+ \frac{1}{2!}\sum_{j\neq i}\sum_{r\neq i,j} {}^{ijr}\varepsilon_0 \Delta < {}^{j}y > \Delta < {}^{r}y > + \cdots .\end{aligned} \tag{A.4}$$

In the "mean reference" under linkage equilibrium, the mean epistasis factors before selection are unity. Using this and (A.1), we obtain

$$\begin{aligned}\Delta < {}^{g\to i}f > &= 2\beta \sum\nolimits_{j\neq i} {}^{ij}\varepsilon_0\, {}^{j}V_{\mathrm{A}} \\ &\quad + \frac{1}{2!}(2\beta)^2 \sum_{j\neq i}\sum_{r\neq i,j} {}^{ijr}\varepsilon_0\, {}^{j}V_{\mathrm{A}}\, {}^{r}V_{\mathrm{A}} + \cdots \\ &= \beta\, {}^{i}\varepsilon V_{\mathrm{A}} + \frac{1}{2!}\beta^2\, {}^{i}\tau V_{\mathrm{A}}^2 + \cdots .\end{aligned} \tag{A.5}$$

Thus, the change in the epistasis factor acting on a particular locus depends on the directionality of epistasis computed by weighting with the evolvability of the interacting loci. If highly evolvable loci have a directional effect on the focal locus, then the epistasis factor of that locus is likely to change. The change in the additive genetic variance due to changes in the epistasis factors alone is given as

$$\begin{aligned}\Delta V_{\mathrm{A}} &= 2\sum\nolimits_i (1 + \Delta < {}^{g\to i}f >)^2\, {}^{i}V_{\mathrm{A}} - V_{\mathrm{A}} \\ &= 2\sum\nolimits_i (2\Delta < {}^{g\to i}f > + \Delta < {}^{g\to i}f >)^2\, {}^{i}V_{\mathrm{A}} \\ &= 4\sum\nolimits_i \Delta < {}^{g\to i}f > {}^{i}V_{\mathrm{A}} + 2\sum\nolimits_i (\Delta < {}^{g\to i}f >)^2\, {}^{i}V_{\mathrm{A}}.\end{aligned} \tag{A.6}$$

Fitting (A.5) into (A.6), and leaving the second term unexpanded we get

$$\Delta V_A = 2\beta\varepsilon V_A^2 + \frac{2}{2!}\beta^2\tau V_A^3 + \cdots + 2\sum\nolimits_i (\Delta < {}^{g\to i}f >)^2\, {}^iV_A. \quad (A.7)$$

The unexpanded term is

$$2\sum\nolimits_i (\Delta < {}^{g\to i}f >)^2\, {}^iV_A = 2\beta^2 V_A^2 \sum\nolimits_i {}^i\varepsilon^2\, {}^iV_A + o(\beta^2) = \beta^2\omega^2 V_A^3 + o(\beta^2). \quad (A.8)$$

Thus the leading terms in the change of additive variance due to epistasis are

$$\Delta V_A = 2\beta\varepsilon V_A^2 + \beta^2(\tau+\omega^2)V_A^3 + o(\beta^2). \quad (A.9)$$

Returning to incorporate the effects of changes in allelic variances, we observe that the total change in additive variance consists of the sum of the effects of epistasis, changes in allelic variances, and an interaction between the two as follows

$$\begin{aligned}\Delta V_A &= 2\sum\nolimits_i (1+\Delta < {}^{g\to i}f >)^2 ({}^iV_A + \Delta\, {}^iV_A) - V_A \\ &= 2\sum\nolimits_i (2\Delta < {}^{g\to i}f > + (\Delta < {}^{g\to i}f >)^2)\, {}^iV_A \\ &\quad + 2\sum\nolimits_i \Delta\, {}^iV_A + 2\sum\nolimits_i (2\Delta < {}^{g\to i}f > \\ &\quad + (\Delta < {}^{g\to i}f >)^2)\Delta\, {}^iV_A. \end{aligned} \quad (A.10)$$

Using (A.3) and (A.9), we get

$$\begin{aligned}\Delta V_A &= 2\beta\varepsilon V_A^2 + \beta^2(\tau+\omega^2)V_A^3 \\ &\quad + 2\beta\sum\nolimits_i {}^iC_3 - 2\beta^2\sum\nolimits_i {}^iV_a^2 + 4\beta^2 V_A \sum\nolimits_i {}^i\varepsilon\, {}^iC_3 \\ &\quad + o(\beta^2), \end{aligned} \quad (A.11)$$

where all quantities are measured with reference to the mean genotype.

Appendix B. Effects of epistasis on long-term response

We have shown that only directional epistasis affects the single-generation response to selection. The simulation results indicate that this also holds true over many generations. In this appendix we provide some insight into why this is so.

To do this we assume only pairwise interactions, and weak selection so that only terms to the lowest order of β are included. Then the change in the additive genetic variance is given by

$$\Delta V_A = 2\beta(\varepsilon V_A^2 + \sum\nolimits_i {}^iC_3) = 2\beta(4\sum\nolimits_i \sum\nolimits_{j\neq i} {}^{ij}\varepsilon_0\, {}^iV_A\, {}^jV_A + \sum\nolimits_i {}^iC_3). \quad (B.1)$$

We now consider how the change in the variance itself changes over time. I.e. we compute the change of the change of variance. Under weak selection, this is

$$\Delta[\Delta V_A] = 2\beta^2(4\omega^2 V_A^3 + 7V_A\sum\nolimits_i {}^i\varepsilon\, {}^iC_3 + \sum\nolimits_i {}^iC_4). \quad (B.2)$$

The calculation will be given later in the appendix. Eq (B.2) shows that changes in the changes of the additive genetic variance are affected predominantly by (locus-) directional forms of epistasis. This clarifies why locus-directional epistasis has relatively strong effects on long-term dynamics. Non-directional epistasis does not enter even into the second-order dynamics. This argument can be extended to higher-order changes of changes, but as the equations become unwieldy, we do not calculate this explicitly, but instead present a proof that every term in the higher-order changes of changes is either additive or proportional to a measure of (locus-) directional epistasis. Thus, if there is no (locus-) directional epistasis, only the additive terms remain.

Formally, we want to prove that under weak selection each term in the kth order of change, $\Delta^k[V_A]$, is either a kth order cumulant, ${}^iC_k$, or an epistatic function, polynomial in ${}^{ij}\varepsilon$, which contain at least one factor of the form ${}^iE_m = \Sigma_{j\neq i}\, {}^{ij}\varepsilon_0\, {}^jC_m$ for some locus i and some $m \leqslant k$. We also assume that all ${}^{ij}\varepsilon_0$ are bounded (i.e. no locus is completely canalized).

The terms ${}^iE_m$ are measures of locus-directional epistasis weighted by cumulants of the locus distribution. Note that ${}^i\varepsilon V_A = 2\, {}^iE_2$.

We prove this by induction. Eqs. (B.1) and (B.2) demonstrate that it holds for first- and second-order change. If it holds true for $\Delta^k[V_A]$ we show that it must then also be true for $\Delta^{k+1}[V_A]$. Consider first the change in the additive terms. By calculation we find

$$\Delta\, {}^iC_k = \beta({}^iC_{k+1} + k\, {}^i\varepsilon V_A\, {}^iC_k) + o(\beta). \quad (B.3)$$

Thus, only terms containing factors of the required sort are generated. By assumption, any of the epistatic terms can be written as ${}^iE_mR(k)$ for some i and some $m \leqslant k$, such that the residual factor $R(k)$ is a polynomial in the epistasis coefficients. The change in these terms can be written as $\Delta[{}^iE_mR(k)] = {}^iE_m\Delta R(k) + R(k)\Delta {}^iE_m + o(\beta)$. The first part contains a factor ${}^iE_m$ (which does not cancel, since $\Delta R(k)$ must be a polynomial under weak selection). Thus, it only remains to show that terms in $\Delta\, {}^iE_m$ contain the required factors.

$$\Delta\, {}^iE_m = \sum\nolimits_{j\neq i} \Delta[{}^{ij}\varepsilon_0\, {}^jC_m] = \sum\nolimits_{j\neq i} [{}^{ij}\varepsilon_0 \Delta\, {}^jC_m + {}^jC_m \Delta\, {}^{ij}\varepsilon_0] + o(\beta). \quad (B.4)$$

We first compute the change in the mean-referenced epistasis coefficient by use of Eq. (3) in the main text.

$$\Delta\, {}^{ij}\varepsilon_0 = \frac{{}^{ij}\varepsilon_0}{({}^{\bar g\to i}f_0 + \Delta\, {}^{\bar g\to i}f_0)({}^{\bar g\to j}f_0 + \Delta\, {}^{\bar g\to j}f_0)} - {}^{ij}\varepsilon_0 = \beta V_A\, {}^{ij}\varepsilon_0({}^i\varepsilon + {}^j\varepsilon) + o(\beta). \quad (B.5)$$

Where we used (A.6) to compute the change in the epistasis factor. The subscribed zero on the epistasis factors emphasize that they are measured with reference to the mean genotype, so that ${}^{\bar{g}\to i}f_0$ is unity. Fitting (B.3) and (B.5) into (B.4) gives

$$\Delta\, {}^{i}E_m = \beta\, {}^{i}E_{m+1} + (m+1)\beta V_{\mathrm{A}}\, {}^{i}\varepsilon\, {}^{i}E_m + \beta\sum\nolimits_{j\neq i}[{}^{ij}\varepsilon_0\, {}^{j}C_m\, {}^{i}\varepsilon\, V_{\mathrm{A}}] + \mathrm{o}(\beta). \tag{B.6}$$

Since ${}^{j}\varepsilon V_A = 2\, {}^{j}E_2$, all terms contain a factor ${}^{i}E_{\mathrm{m}}$ for some i and m.

To compute (B.2), we note that $\Delta V_{\mathrm{A}} = 2\beta\sum_i[{}^{i}C_3 + 4\, {}^{i}V_{\mathrm{A}}\, {}^{i}E_2]$, and we can write

$$\begin{aligned}\Delta[\Delta V_{\mathrm{A}}] &= 2\beta\sum\nolimits_i[\Delta\, {}^{i}C_3 + 4\, {}^{i}E_2\Delta\, {}^{i}V_{\mathrm{A}} + 4\, {}^{i}V_{\mathrm{A}}\Delta\, {}^{i}E_2] + \mathrm{o}(\beta)\\ &= 2\beta^2\sum\nolimits_i[{}^{i}C_4 + 14\, {}^{i}E_2\, {}^{i}C_3 + 32\, {}^{i}E_2{}^{2}\, {}^{i}V_{\mathrm{A}}] + \mathrm{o}(\beta^2),\end{aligned} \tag{B.7}$$

where we have used (B.3) and (B.6) to calculate the final result. By comparing definitions of the various elements, (B.7) can be seen to equal (B.2). These calculations suggest that the long-term dynamics are determined by the cumulants of the allelic distributions, ${}^{i}C_k$, and by the epistatic functions, ${}^{i}E_k$.

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