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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