# *Effects of genetic drift on variance components under a general model of epistasis*

N. H. Barton[*+] and Michael Turelli[+]

*Institute of Cell, Animal and Population Biology

University of Edinburgh

EH9 3JT U.K.

[+] Section of Evolution and Ecology

University of California

Davis CA 95616 U.S.A.

Running head: Epistasis made simple
Key words: population bottlenecks, additive variance, quantitative genetics, shifting balance, multilocus diffusion approximations, adaptation
Corresponding author: Nick Barton
Address: Institute of Cell, Animal and Population Biology
University of Edinburgh
West Mains Road
Edinburgh EH9 3JT
Scotland

Phone: +44 (0) 131 650 5509
Fax: +44 (0) 131 667 3210
Email: n.barton@ed.ac.uk

**Abstract**

We analyze the changes in the mean and variance components of a quantitative trait caused by changes in allele frequencies, concentrating on the effects of genetic drift. We use a general representation of epistasis and dominance that allows an arbitrary relation between genotype and phenotype for any number of diallelic loci. We assume initial and final Hardy-Weinberg and linkage equilibrium in our analyses of drift-induced changes. Random drift generates transient linkage disequilibria that cause correlations between allele frequency fluctuations at different loci. However, we show that these have negligible effects, at least for interactions among small numbers of loci. Our analyses are based on diffusion approximations that summarize the effects of drift in terms of $F$, the "inbreeding coefficient," interpreted as the expected proportional decrease in heterozygosity at each locus. For haploids, the variance of the trait mean after a population bottleneck is $\mathrm{var}(\Delta \bar{z}) = \sum_{k=1}^{n} F^k V_{A(k)}$, where $n$ is the number of loci contributing to the trait variance, $V_{A(1)} = V_A$ is the additive genetic variance, and $V_{A(k)}$ is the $k$th-order additive epistatic variance. The expected additive genetic variance after the bottleneck, denoted $\langle V_A^* \rangle$, is closely related to $\mathrm{var}(\Delta \bar{z})$; $\langle V_A^* \rangle = (1-F) \sum_{k=1}^{n} k F^{k-1} V_{A(k)}$. Thus, epistasis inflates the expected additive variance above $V_A(1-F)$, the expectation under additivity. For haploids (and diploids without dominance), the expected value of every variance component is inflated by the existence of higher-order interactions (e.g., third-order epistasis inflates $\langle V_{\mathrm{AA}}^* \rangle$). This is not true in general with diploidy, because dominance alone can reduce $\langle V_A^* \rangle$ below $V_A(1-F)$ (e.g., when dominant alleles are rare). Without dominance, diploidy produces simple expressions: $\mathrm{var}(\Delta \bar{z}) = \sum_{k=1}^{n} (2F)^k V_{A(k)}$ and $\langle V_A^* \rangle = (1-F) \sum_{k=1}^{n} k (2F)^{k-1} V_{A(k)}$. With dominance (and even without epistasis), $\mathrm{var}(\Delta \bar{z})$ and $\langle V_A^* \rangle$ no longer depend solely on the variance components in the base population. For small $F$, the expected additive variance simplifies to $\langle V_A^* \rangle \simeq (1-F) V_A + 4FV_{\mathrm{AA}} + 2FV_D + 2FC_{\mathrm{AD}}$, where $C_{\mathrm{AD}}$ is a sum of two terms describing covariances between additive effects and dominance and additive-by-dominance interactions. Whether population bottlenecks lead to expected increases in additive variance depends primarily on the ratio of nonadditive to additive genetic variance in the base population, but dominance precludes simple predictions based solely on variance components. We illustrate these results using a model in which genotypic values are drawn at random, allowing extreme and erratic epistatic interactions. Although our analyses clarify the conditions under which drift is expected to increase $V_A$, we question the evolutionary importance of such increases.

## Introduction

Epistasis, interpreted as nonadditive effects of alleles at distinct loci, has been acknowledged as common for polygenic traits since Fisher (1918) reconciled Mendelian inheritance with biometrical analyses of similarities between relatives. Epistasis for fitness is essentially inescapable and has been explicit in every model of selection on polygenic traits since Wright's (1935) pioneering treatment of stabilizing selection (Coyne et al. 1997, 2000). The role of epistatic interactions in producing hybrid inviability and sterility was popularized by Dobzhansky (1937) and Muller (1940), but was understood as important for the origin of reproductive isolation even earlier (e.g., Poulton 1908, Ch. II). Nevertheless, there are persistent laments that epistasis is ignored or that if its ubiquity were acknowledged, evolutionists would embrace drift-based theories of adaptation and/or speciation in which epistasis plays some role (e.g., Wade and Goodnight 1998, Cheverud 2000, Templeton 2000, Wade 2000). Part of the mystique surrounding epistasis is that it remains extremely difficult to analyze mathematically.

Recent descriptions of particular patterns of epistasis elucidate the maintenance of variation (e.g., Hermisson et al. 2003) and patterns of postzygotic isolation (e.g., Turelli and Orr 2000); and Barton and Turelli (1991) introduced a general mathematical framework for analyzing epistatic selection. Yet, until some recent work by Wagner and his associates (e.g., Wagner et al. 1998, Hansen and Wagner 2001), the mathematical language used by quantitative geneticists to discuss multilocus epistasis had not advanced significantly since Cockerham (1954) and Kempthorne (1954) elaborated Fisher's (1918) original treatment. Although Cockerham (1954) and Kempthorne (1954) treated *n*-locus interactions, their notation is so complex and the resulting algebra so challenging that most applications have reverted to extrapolations from two-loci (e.g., Cockerham and Tachida 1988). In this paper, we describe epistasis by adapting the mathematical framework for multilocus selection introduced by Barton and Turelli (1991) and extended by Kirkpatrick et al. (2002). We show how this framework provides an efficient language for describing arbitrary epistatic interactions that simplifies the algebra so that some difficult questions become analytically tractable. Our notation for describing general patterns of epistasis for diallelic loci seems to provide more transparent solutions for the problems we discuss than the more elaborate notation suggested by Hansen and Wagner (2001). We illustrate our approach by analyzing drift-induced changes in the mean and variance components of quantitative traits, even though we remain skeptical that such changes are significant for either adaptation or speciation.

In several experiments, the estimated additive genetic variance has increased after severe reductions in population size, $N$ (e.g., Bryant et al. 1986, Lopez-Fanjul and Villaverde 1989, Cheverud et al. 1999; reviewed by Walsh and Lynch 1998). This has seemed paradoxical, because genetic drift must, on average, reduce heterozygosity at the underlying loci. However, additive genetic variance may nevertheless increase if the additive effects of alleles increase. This may happen through dominance, because the additive effects of recessive alleles will increase if they become more common (Robertson 1952, Willis and Orr 1993). Epistatic effects can also lead to increasing additive variance as allele-frequency changes modify additive effects (Cockerham 1984; Goodnight 1987, 1988; Cockerham and Tachida 1988). Drift-induced inflation of additive genetic variance has received considerable attention, and we provide a skeptical review of its proposed biological significance in our Discussion. However, our mathematical framework describes the effects of arbitrary allele frequency changes on quantitative traits, regardless of what causes those changes.

In this paper, we set out a simple analysis of how the mean phenotype and variance components change as a result of random drift of allele frequencies. By neglecting selection, we can reach quite general conclusions. This seems a reasonable assumption, since drift will dominate during a brief population bottleneck. We concentrate on allele frequency changes, assuming that the initial and final populations are at linkage equilibrium. Again, this seems reasonable for most outcrossing organisms, since genes will usually be loosely linked, and so for isolated populations only very strong epistasis generates significant linkage disequilibrium. Transient linkage disequilibria will be generated by drift, but these will soon dissipate. We argue using both analytical approximations and exact multilocus simulations that these transient disequilibria have negligible effects on the pattern of allele frequency fluctuations, which are of primary importance.

- **Relation to previous analyses**

In classical quantitative genetics, the phenotype is represented as a sum of effects, each attributed to a certain set of genes. (Additive effects are due to single genes, dominance effects to pairs of homologous genes in a diploid, pairwise epistatic effects involve contributions from alleles or genotypes at pairs of loci, and so on.) These effects are defined with respect to a base population, such that the different effects are uncorrelated (at linkage equilibrium), and the total genotypic variance is the sum of the variances of each effect ($V_G = V_A + V_D + V_{\mathrm{AA}} \ldots$). Variances and covariances between individuals are given by a sum of terms, each term being weighted by identity coefficients that give the probabilities that various *sets* of genes are identical by descent from the base population. In certain cases, this sum involves only variance components – for example, covariances between relatives within a base population that is in Hardy-Weinberg and linkage equilibrium, with no linkage (Kempthorne 1954, Cockerham 1954). However, in general it involves complicated moments of the distribution of effects in the base population.

The effects of drift have been analyzed in detail for two loci. For the general case with linkage between the loci, and with linkage disequilibrium in the inbred population, many different identity coefficients must be defined. Explicit formulae for these coefficients are cumbersome, but it is straightforward to calculate them using linear recursions. Goodnight (1987, 1988) derived the effect of a single-generation bottleneck and of continued drift on the expected additive genetic variance, and found that this would increase for small $F$ if the additive genetic variance is smaller than three times the additive×additive epistatic variance ($V_A < 3\,V_{AA}$, neglecting $V_D$). Goodnight's results included the linkage disequilibria generated by drift, which will contribute to genetic variance immediately after the bottleneck. Cockerham and Tachida (1988) calculated the effects on additive genetic variance that persist after these linkage disequilibria dissipate. They found that in the absence of dominance, additive genetic variance will increase in the long term if $V_A < 4\,V_{AA}$. However, other coefficients contribute, and the effects cannot be written solely in terms of variance components. More complex population structures have been analyzed, including migration and extinction/recolonization (Tachida and Cockerham 1989, Whitlock et al. 1993).

All these results are essentially two-locus analyses; moreover, they do not include additive×dominance or dominance×dominance effects, and so do not give a complete analysis even of two loci. (Cheverud and Routman (1996) do include these effects, but their approach is wholly numerical and is restricted to intermediate initial allele frequencies.) The available analytical results apply to multiple loci only if dominance and higher-order additive

contributions to the phenotype are neglected. The general approach based on identity-by-descent becomes intractable beyond two loci, because it is necessary to follow large numbers of identity coefficients. (With linkage disequilibrium, one must specify the joint probability of identity of *sets* of genes at multiple loci. For example, the probability that genes $\{i_1,\ i_2,\ i_3\}$ are identical by descent (abbreviated i.b.d.) at locus $i$, and that genes $\{j_1,\ j_2\}$ but not $j_3$ are i.b.d. at locus $j$ could be written $F_{\{\{\{i_1,i_2,i_3\}\},\{\{j_1,j_2\},\{j_3\}\}\}}$; see Appendix 2.) Moreover, these multilocus identity coefficients have traditionally been defined in an idiosyncratic way, so that it is not possible to write down explicit multilocus formulas.

Our analytical approach provides a way to test simulation-based conjectures and to explain some interesting experimental observations. For instance, in a heroic set of highly replicated bottleneck experiments, Cheverud et al. (1999) demonstrated that although additive variance increased rather rarely, the observed additive variance was generally in excess of the reduced expectation under additivity. We show that without dominance, epistasis systematically inflates $\langle V_A^* \rangle$, expected additive genetic variance after a bottleneck, above the additive expectation, $(1 - F)\, V_A$, for all diallelic epistatic systems. In contrast, dominance can increase or decrease $\langle V_A^* \rangle$. Our framework, which complements that of Hansen and Wagner (2001), should facilitate additional analyses of the consequences of epistasis.

## The model

Suppose a trait is determined in an arbitrary way by $n$ diallelic loci. For simplicity, we assume random mating and no selection. We also assume that there is no sex-dependence of phenotypes and no effect of the parental origin of alleles (i.e., no cis-trans effects or maternal effects). We illustrate some ideas with haploids, but our analysis includes diploidy. When analyzing the consequences of population bottlenecks, we assume that changes in allele frequencies can be approximated by a diffusion. This implies that the pattern of population sizes during the bottleneck influences the final distribution of allele frequencies only through a single parameter, the net inbreeding coefficient $F$. (In the diffusion approximation, time can be rescaled relative to the current rate of drift, so that an arbitrary pattern of population size is transformed to a standard form.) We show that this approximation is quite accurate even for severe bottlenecks.

We begin by setting out an explicit representation of epistasis and dominance, in which the phenotype is written as a polynomial function of variables that describe the genotype. Assuming Hardy-Weinberg and linkage equilibrium (HWLE), we show that the coefficients of this polynomial are just the additive, dominance, and higher-order interaction effects of

classical quantitative genetics. We next show how these effects, the mean and the variance components change as allele frequencies change, giving general expressions that apply to haploids and diploids. Understanding the implications of these changes is greatly simplified by assuming that allele frequency fluctuations are independent across loci and that the initial and final populations are in HWLE. It is reasonable to assume linkage equilibrium, because strong selection and/or tight linkage are needed to maintain significant linkage disequilibrium in the base population, and any disequilibrium generated by drift will quickly dissipate unless linkage is tight. Results for haploids, or for diploids in the absence of dominance, follow directly and depend only on the variance components in the base population. However, dominance introduces substantial complications, so that expected values for the population mean and additive variance no longer depend solely on the variance components. Nevertheless, we obtain an explicit, fairly compact expression that describes how the additive variance changes for small $F$. Moreover, for the general model, we show that epistasis inflates the expected additive variance after drift above the value expected under complete additivity. To illustrate the general results with extremely complex epistasis, we provide simulation results for a model in which genotypic values are chosen at random (similar to Naciri-Graven and Goudet 2003). Analytical results concerning this model will be published separately.

Even if the initial and final populations are at linkage equilibrium, transient disequilibria do influence the final distribution of allele frequencies. For example, if there is a large fluctuation in allele frequency at one locus, then there is likely to be a large fluctuation at a linked locus. (That is, there is a covariance between the squared deviations of allele frequencies at linked loci.) We derive expressions for these associations, and show that they have little influence even with tight linkage (Appendix 2). These analytical results, together with explicit multilocus simulations under extreme epistasis, support our assumption that the post-bottleneck distributions of allele frequencies at different loci are statistically independent.

■ **Notation**

Our notation follows that introduced by Barton and Turelli (1991) and extended by Kirkpatrick et al. (2002). Loci are labelled $i$, $j$, $k\ldots$ In diploids, genes are denoted with subscripts, e.g., $i_m$, $i_f$, to indicate paternal versus maternal origin. A gene and its parental origin is termed a *position*, and denoted by double-struck font (e.g., $\mathbb{i} = i_m$). The distinction between genetic loci and positions is crucial when we define components of variance in diploids. The state of each position is denoted by $X_{\mathbb{i}}$; for diallelic loci, we set $X_{\mathbb{i}} =$ 0 or 1. The corresponding frequency of allele 1 is $p_{\mathbb{i}} = E[X_{\mathbb{i}}]$, where $E[\,]$ denotes an expectation over the distribution of genotypes in the population. We assume equal allele frequencies in the sexes, so that allele frequency depends only on the locus, $i$, and can be written $p_i$. (With drift, allele frequencies differ randomly between the sexes. However, under the diffusion approximation, these differences are negligible.)

Linkage disequilibria are defined relative to a *reference point*, which might be either the allele frequencies in the initial population or the current population. Deviations from the reference point are denoted $\zeta_{\mathbb{i}} = X_{\mathbb{i}} - p_{\mathbb{i}}$, and products of those deviations over sets of positions, $\mathbb{U}$, are denoted compactly by $\zeta_{\mathbb{U}}$. We set $E[\zeta_{\mathbb{U}}] = D_{\mathbb{U}}$. The set of all relevant positions in an individual is denoted $\mathbb{Z}$.

For example, for a trait determined by two loci in a haploid, $\mathbb{Z} = \{1,\ 2\}$; and a population can be described by three variables: $D_{\{1\}}$, $D_{\{2\}}$, and $D_{\{1,2\}}$. The first two are the differences in allele frequency between the population in question and the reference population ($D_{\{1\}} = \Delta p_1$, $D_{\{2\}} = \Delta p_2$). $D_{\{1,2\}}$ is a measure of linkage disequilibrium, defined with respect to the reference allele frequencies. If we choose to change the reference point to the new allele frequencies, then using superscript * to denote the new values, $D^*_{\{1\}} = 0$, $D^*_{\{2\}} = 0$, and $D^*_{\{1,2\}} = D_{\{1,2\}} - \Delta p_1\, \Delta p_2$ is the standard coefficient of linkage disequilibrium. For compactness, we abbreviate variables such as $D_{\{i,j\}}$ by $D_{ij}$.

In a diploid, there are two positions at each autosomal locus. Thus, for loci $i$ and $j$, we must consider sets of positions of the form $\mathbb{Z} = \{i_m,\ j_m,\ i_f,\ j_f\}$. In a diploid population, the state of these two loci is defined by 15 coefficients, corresponding to the 15 non-empty subsets of $\mathbb{Z}$. However, under random union of gametes and no differences between the sexes, these reduce to the same three variables that describe the haploid gamete pool:
$D_{i_m} = D_{i_f} = \Delta p_i$, $D_{j_m} = D_{j_f} = \Delta p_j$, $D_{i_m\, j_m} = D_{i_f\, j_f} = D_{ij}$, whereas
$D_{i_m\, i_f} = (\Delta p_i)^2$, $D_{j_m\, j_f} = \left(\Delta \mathrm{p}_j\right)^2$, $D_{i_m\, j_f} = D_{i_f\, j_m} = \Delta \mathrm{p}_i\, \Delta \mathrm{p}_j$,
$D_{i_m\, j_m\, i_f} = D_{i_f\, j_f\, i_m} = D_{ij}\, \Delta \mathrm{p}_i$, $D_{i_m\, j_m\, j_f} = D_{i_f\, j_f\, j_m} = D_{ij}\, \Delta \mathrm{p}_j$, and $D_{i_m\, j_m\, i_f\, j_f} = D^2_{ij}$.

■ **Description of epistasis and consequences of changing reference points**

In general, a polygenic trait can be written as a polynomial function of the allelic states

$$z = \bar{z} + \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} b_{\mathbb{U}} \, (\zeta_{\mathbb{U}} - D_{\mathbb{U}}), \qquad (1)$$

where $\zeta_i \equiv x_i - p_i$, $\zeta_{\mathbb{U}} \equiv \prod_{i \in \mathbb{U}} \zeta_i$, $D_{\mathbb{U}} \equiv E[\zeta_{\mathbb{U}}]$, $\mathbb{Z}$ is the set of all positions in an individual, and the sum in Eq. 1 is over all nonempty subsets $\mathbb{U}$ of $\mathbb{Z}$ with only one permutation of any subset included in the summation (i.e., we do not count $\{i_m, j_m\}$ and $\{j_m, i_m\}$ as separate sets). As described below, the terms $b_{\mathbb{U}}$ depend on both the physiological mapping from genotypes to phenotypes (i.e., the genotypic values for all genotypes) and the allele frequencies used as reference points. For any specific genotype, e, and assuming two alleles, each $X_i$ is 0 or 1 and Eq. 1 specifies its genotypic value. We will use the general convention that sums over subsets include the null set ($\emptyset$), unless it is explicitly excluded (as in Eq. 1). In the sets $\mathbb{U}$, each position index appears at most once; and the permutations of the set of indices that appear in a particular set do not appear as separate elements of the sum. Nevertheless, expectations over sets involving repeated indices arise in calculations below, but the corresponding moments can be calculated simply for diallelic loci (see Eq. 5 of Barton and Turelli 1991). With two alleles, $D_{ii} = p_i q_i$. Similarly, for any set $\mathbb{U}$ that contains no repeated indices, $D_{\mathbb{U}\mathbb{U}} \equiv E[\prod_{i \in \mathbb{U}} \zeta_i^2] = \prod_{i \in \mathbb{U}} p_i q_i$. We denote the product $\prod_{i \in \mathbb{U}} p_i q_i$ by $pq_{\mathbb{U}}$.

The coefficients $b_{\mathbb{U}}$ in Eq. 1 depend on the reference allele frequencies. As shown below, it is simple to go from one reference point to another, expressing the new coefficients in terms of the old. By comparing two reference points, we can use our notation to discuss the relationship between "physiological" or "functional" epistasis and "statistical" epistasis for any number of loci and any pattern of gene interaction. This distinction has been used in at least two distinct ways: by Cheverud and Routman (1995, 1996) to emphasize that epistatic variance components may be small even when non-additive interactions among segregating loci are extreme (e.g., Crow and Kimura 1970, Table 4.1.3; Keightley 1989) and by Hansen and Wagner (2001) to distinguish between non-additive interactions between alleles at different loci when effects are measured as i) departures from the mean phenotype produced by a reference genotype and ii) the traditional quantitative genetic definition of epistasis in which departures are measured relative to the mean of a population segregating at several loci. It is unquestionably important to realize that both variance components and epistatic effects depend on population composition. However, as made clear by Eq. 3 below and by Hansen and Wagner's (2001) Result 2.1, any *quantification* of epistasis is essentially arbitrary, because a specific reference must be used to quantify the departures from additivity. Once this is

appreciated, it makes little difference whether one uses a fixed reference genotype, as proposed by Hansen and Wagner (2001), a weighted average of genotypic effects, as proposed by Cheverud and Routman (1995), or a segregating population with specific allele frequencies, as proposed by Fisher (1918), to quantify epistatic effects. We will contrast the reference point in which all loci are fixed for the 0 allele (equivalent to choosing a reference genotype with all 0 alleles), so that $p_i = 0$ for all *i,* with a reference point corresponding to the allele frequencies in a polymorphic population. In the former case, the coefficients $b_{\mathbb{U}}$ correspond to Hansen and Wagner's (2001) "functional" interactions between the positions in $\mathbb{U}$; whereas in the latter case, the $b_{\mathbb{U}}$ describe statistical effects produced by those interactions and the current allele frequencies.

Our notation shows that the existence of particular levels of interaction, e.g., dominance, additive-by-additive versus additive-by-dominance epistasis, is generally independent of the reference point chosen; whereas for a fixed level of biological interaction (as revealed by examination of *any* reference point), the magnitude of lower-order effects must be reference-point dependent. To illustrate this idea simply, consider biallelic haploids, so that $\mathbb{Z} = \{1, 2, ..., n\}$ and the $b_{\mathbb{U}}$ have the form $b_{ijk...}$, with all subscripts distinct. As argued by Hansen and Wagner (2001), one way to think about physiological or functional interactions is to focus on a specific genotype, then ask how changing each allele in turn (and changing them in all combinations) alters the mean phenotype. Using the reference genotype with 0 alleles at all loci corresponds to $p_i = 0$ for all $i$ in (1), and $\bar{z}$ is just the genotypic value for (0, 0, ..., 0), denoted $G_{\mathbf{0}}$. With this starting point, each $b_i$ describes the change in the mean phenotype when allele 1 is introduced at locus $i$ and nowhere else. The terms $b_{ij}$ describe the additional effect on the mean phenotype of having 1 alleles at both loci $i$ and $j$ that cannot be explained by $b_i + b_j$. Thus, $b_{ij} \neq 0$ if and only if there is additive-by-additive interaction between loci i and j. Similarly, $b_{ijk}$ describes three-way effects not accounted for by lower-order terms (namely, $b_i + b_j + b_k + b_{\mathrm{ij}} + b_{\mathrm{ik}} + b_{\mathrm{jk}}$), etc. This representation applies to any pattern of epistasis. In the haploid case, there are $2^n$ genotypes and our representation has $2^n$ free parameters: the initial constant, $G_{\mathbf{0}}$; the $n$ allelic effect terms, $b_i$; the $\binom{n}{2}$ pairwise interaction terms, etc. (these numbers are simply the terms in the binomial expansion of $(1 + 1)^n$). Nevertheless, the specific values obtained for these coefficients have no intrinsic physiological or functional meaning because they depend on the reference point.

To see this, we show for both haploids and diploids how to find the new set of coefficients, $b^*_{\mathbb{U}}$, that define the relation between genotype and phenotype when the reference point is changed from $p_i$ to $p^*_i = p_i + \Delta p_i$. The old deviation $\zeta_{\mathbb{i}} = X_{\mathbb{i}} - p_{\mathbb{i}}$ can be rewritten as $\zeta_{\mathbb{i}} = \zeta^*_{\mathbb{i}} + \Delta p_{\mathbb{i}}$. Thus, Eq. 1 implies

$$\begin{aligned} z &= \bar{z} + \sum_{\mathbb{U} \neq \varnothing} b_{\mathbb{U}} \left( \prod_{\mathbb{i} \in \mathbb{U}} (\zeta^*_{\mathbb{i}} + \Delta p_{\mathbb{i}}) - E\Big[ \prod_{\mathbb{i} \in \mathbb{U}} (\zeta^*_{\mathbb{i}} + \Delta p_{\mathbb{i}}) \Big] \right) \\ &= \bar{z} + \sum_{\mathbb{U} \neq \varnothing} b_{\mathbb{U}} \sum_{\mathbb{S}+\mathbb{T}=\mathbb{U}} (\zeta^*_{\mathbb{S}} - D^*_{\mathbb{S}}) \, \Delta p_{\mathbb{T}} \, . \end{aligned} \qquad (2)$$

Because $b^*_{\mathbb{V}}$ is defined as the coefficient of $\zeta^*_{\mathbb{V}}$ in the expansion of z, this shows that $b_{\mathbb{U}}$ contributes to $b^*_{\mathbb{V}}$ for all $\mathbb{V} \subseteq \mathbb{U}$. It follows that the coefficients obtained from different sets of reference allele frequencies are related by

$$b^*_{\mathbb{U}} = \sum_{\mathbb{V} \subseteq \mathbb{Z} \setminus \mathbb{U}} b_{\mathbb{U}\mathbb{V}} \, \Delta p_{\mathbb{V}} \qquad (3)$$

(note that this sum includes $\mathbb{V} = \varnothing$), where $\mathbb{Z}\setminus\mathbb{U}$ denotes the set of elements in $\mathbb{Z}$ but not $\mathbb{U}$ and $\mathbb{U}\mathbb{V}$ denotes the union of sets $\mathbb{U}$ and $\mathbb{V}$. Expression (3) is analogous to Result 3.2 of Hansen and Wagner (2001, p. 65). They use individual genotypes as reference points; but their framework allows for multiple alleles under a "multilinearity" assumption, which states that changes in genetic background modify all substitution effects at a locus by the same proportionate factor. In contrast, our analysis is restricted to two alleles; but it uses as reference points any set of allele frequencies and HWLE genotype frequencies. For the class of problems we investigate, our notation, which produces the relatively simple expression (3) for calculating the new coefficients $b_{\mathbb{U}}$ when the reference allele frequencies are changed, seems to provide more general and transparent solutions.

We will show below that the values of $b_{\mathbb{U}}$ defined in terms of current allele frequencies are proportional to the statistical effects, as traditionally defined, of the specified combination of alleles. Hence, Eq. 3 shows that interactions of any specified order contribute in general to statistical effects of the same order and all *lower* orders when the reference point is changed. In particular, three-way interactions in one frame of reference will contribute to both pairwise interaction effects and mean effects of individual alleles. However, if in any frame of reference, we find, for instance, no interactions involving more than two alleles, then Eq. 3 shows that no such interactions will exist in any other frame of reference. In this sense, the *existence* of a specific level of epistasis is "functionally" defined by the mapping of genotypes onto average phenotypes. The converse, however, is not true. For instance, if

additive-by-additive epistasis exists, the values of lower-order terms, and in particular, whether they are non-zero, depend on the reference point chosen. (Note that we only consider shifts of reference point here. Nonlinear scale transformations generate higher-order interactions, giving another sense in which measures of epistasis are arbitrary).

- **Mean effects**

Statistical effects of specific combinations of alleles are defined in terms of deviations from expectations based on contributions from all subsets of those alleles. For instance, the additive effect of an allele is defined as the difference between the average phenotype of individuals carrying that allele and the overall mean; and pairwise effects are defined as the difference between the average phenotype of individuals carrying both alleles and the sum of the overall mean and the average effects of the individual alleles, etc. Hence, the general calculation of interest in defining statistical effects is the expected value of z conditional on a specific set of alleles. Despite the change in notation, our derivation is a special case of Kempthorne's (1957, Ch. 19), which allows multiple alleles. Like his, our treatment applies only for Hardy-Weinberg and linkage equilibrium: with associations among loci ($D_{\mathbb{U}} \neq 0$), our $b_{\mathbb{U}}$ are no longer equivalent to the deviations defined in terms of conditional expectations (see Barton and Turelli 1991, p. 249).

To calculate expected deviations for a population in HWLE, first note that representation Eq. 1 simplifies when using the current allele frequencies as our reference point because $D_{\mathbb{U}} = 0$ for all $\mathbb{U}$. Thus,

$$z = \bar{z} + \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} b_{\mathbb{U}} \zeta_{\mathbb{U}}. \qquad (4)$$

In general, we want to calculate the average deviation from the population mean of individuals carrying allele $X_i = 1$ at the set of positions $i \in \mathbb{S}_1$, and $X_i = 0$ for $i \in \mathbb{S}_0$, then ask how much of that deviation cannot be explained by the effects of alleles associated with all subsets of those positions. To simplify the notation, for any function $f$ of the $X_i$ and any disjunct sets of positions $\mathbb{S}_0$ and $\mathbb{S}_1$, we define the conditional expectations

$$E[f \mid \mathbb{S}_0, \mathbb{S}_1] = E[f \mid X_i = 0 \text{ for } i \in \mathbb{S}_0, X_i = 1 \text{ for } i \in \mathbb{S}_1]. \qquad (5)$$

Using (4),

$$E[z \mid \mathbb{S}_0, \mathbb{S}_1] - \bar{z} = \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} b_{\mathbb{U}} E[\zeta_{\mathbb{U}} \mid \mathbb{S}_0, \mathbb{S}_1]. \qquad (6)$$

Under HWLE, all of the elements in the products $\zeta_{\mathbb{U}}$ are independent with mean zero; hence, $E[\zeta_{\mathbb{U}} \mid \mathbb{S}_0, \mathbb{S}_1] = 0$ if $\mathbb{U}$ contains any positions that are not in $\mathbb{S} = \mathbb{S}_0 \bigcup \mathbb{S}_1 \equiv \mathbb{S}_0\,\mathbb{S}_1$. For any nonempty $\mathbb{U} \subseteq \mathbb{S}$, we have $\mathbb{U} = \mathbb{T}_0\,\mathbb{T}_1$, with $\mathbb{T}_0 \subseteq \mathbb{S}_0$, $\mathbb{T}_1 \subseteq \mathbb{S}_1$ and $\mathbb{T}_0\,\mathbb{T}_1 \neq \emptyset$. Hence,

$$E[z \mid \mathbb{S}_0, \mathbb{S}_1] - \bar{z} = \sum_{\mathbb{T}_0 \subseteq \mathbb{S}_0} \sum_{\mathbb{T}_1 \subseteq \mathbb{S}_1} b_{\mathbb{U}}\,(-p)_{\mathbb{T}_0}\,q_{\mathbb{T}_1}\,. \tag{7}$$

Note that this summation involves a highest-order term with $\mathbb{T}_0 = \mathbb{S}_0$ and $\mathbb{T}_1 = \mathbb{S}_1$, plus terms associated with all subsets of positions in $\mathbb{S}_0\,\mathbb{S}_1$. Hence, by definition, the effect term, denoted $\alpha_{\mathbb{S}_o\,\mathbb{S}_1}$, associated with genotypes identified by $\mathbb{S} = \mathbb{S}_0\,\mathbb{S}_1$ is just the highest-order term, namely

$$\alpha_{\mathbb{S}_0\,\mathbb{S}_1} = b_{\mathbb{S}_0\,\mathbb{S}_1}\,(-p)_{\mathbb{S}_0}\,q_{\mathbb{S}_1} \equiv b_{\mathbb{S}}\,(-p)_{\mathbb{S}_0}\,q_{\mathbb{S}_1}\,. \tag{8}$$

This calculation shows that Eq. 1 provides an immediate decomposition of each genotypic value into additive effects of alleles, dominance deviations, and all of the second- and higher-order epistatic components. For instance, the additive allelic effect associated with $\mathbb{S}_0 = \{i_m\}$ is just $-b_{i_m}\,p_i$, the dominance deviation associated with $\mathbb{S}_0 = \{i_m\}$, $\mathbb{S}_1 = \{i_f\}$ is $-b_{i_m\,i_f}\,p_i\,q_i$, and the additive-by-additive effect associated with $\mathbb{S}_1 = \{i_m, j_f\}$ is $b_{i_m\,j_f}\,q_i\,q_j$. Similarly, the effect of a substitution at locus $i$ is just $b_i$, assuming no sex-dependence.

We define the random variable $\alpha_S$ as the average effect of genotypes associated with the positions in $\mathbb{S}$. It follows simply from our notation that $\mathrm{E}[\alpha_S] = 0$. To see this, note that $E[\alpha_S]$ is an average over all genotypes associated with the positions in $\mathbb{S}$, i.e., all disjunct sets $\mathbb{S}_0$ and $\mathbb{S}_1$ such that $\mathbb{S} = \mathbb{S}_0\,\mathbb{S}_1$. The particular genotype indicated by Eq. 8 occurs with frequency $q_{\mathbb{S}_0}\,p_{\mathbb{S}_1}$; hence, this genotype contributes $b_{\mathbb{S}}(-\mathrm{pq})_{\mathbb{S}_0}\,(\mathrm{pq})_{\mathbb{S}_1} = (-1)^{\mathbb{S}_0}\,b_{\mathbb{S}}(\mathrm{pq})_{\mathbb{S}}$ to $E[\alpha_{\mathbb{S}}]$. This shows that each position in $\mathbb{S}$ contributes two terms to $E[\alpha_S]$ (corresponding to $X_i = 0$ or 1) of equal magnitude but opposite sign, producing $E[\alpha_{\mathbb{S}}] = 0$. Thus, computing components of variance reduces to finding $E[\alpha^2_{\mathbb{S}}]$ (a simple, general expression is given in Appendix 1) and summing over the appropriate sets of positions, $\mathbb{S}$.

- **Variance components**

The trait mean in the base population is defined in Eq. 1 as $E[z] = \bar{z}$. Using the current allele frequencies as our reference points, the genotypic variance is

$$\begin{aligned} V_G &= E[(z - \bar{z})^2] = E\Big[\sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} \sum_{\emptyset \neq \mathbb{V} \subseteq \mathbb{Z}} b_{\mathbb{U}}\,b_{\mathbb{V}}\,\zeta_{\mathbb{U}}\,\zeta_{\mathbb{V}}\Big] \\ &= \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} \sum_{\emptyset \neq \mathbb{V} \subseteq \mathbb{Z}} b_{\mathbb{U}}\,b_{\mathbb{V}}\,D_{\mathbb{U}\mathbb{V}}\,. \end{aligned} \tag{9}$$

With HWLE, all associations among distinct sets of positions are zero. Thus, $D_{\mathbb{U}\mathbb{V}}$ is non-zero only if $\mathbb{U} = \mathbb{V}$, in which case $D_{\mathbb{U}\mathbb{U}} = pq_{\mathbb{U}}$. Hence,

$$V_G = \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} b_{\mathbb{U}}^2 \, pq_{\mathbb{U}}. \qquad (10)$$

Equation 10 applies to both haploids and diploids (this is a special case of the calculations in Barton and Turelli (1991) that allow for non-random mating and linkage disequilibrium). The genotypic variance decomposes into components reflecting additive effects, dominance effects, and epistasis of different orders. As shown above, the $b_{\mathbb{U}}$ defined in terms of the current allele frequencies are proportional to the additive, dominance and epistatic effects defined in classical quantitative genetics; and, as expected, the components of Eq. 10 correspond to the variance components traditionally defined in terms of these effects. In Appendix 1, we show how the individual variance components are identified.

For haploids, we have $\mathbb{Z} = \{i, j, k \ldots\}$. From Appendix 1,

$$V_G = V_A + V_{AA} + V_{AAA} \ldots, \text{ where} \qquad (11)$$

$$V_A = \sum_{i \in \mathbb{Z}} b_i^2 \, p_i \, q_i, \; V_{AA} = \sum_{\substack{i,j \in \mathbb{Z} \\ i<j}} b_{ij}^2 \, pq_{ij}, \text{ etc.} \qquad (12)$$

As noted above, we use the convention that the sums over $i \neq j$ count only one of $\{i, j\}, \{j, i\}$, so that the sum in Eq. 12 for $V_{AA}$ is over $\binom{n}{2}$ terms. In general, we can let $V_{A(k)}$ denote the $k$th-order additive interaction ($V_A = V_{A(1)}$, $V_{AA} = V_{A(2)} \ldots$). Then $V_{A(k)}$ can be compactly expressed as

$$V_{A(k)} = \sum_{U: \, |U| = k} b_U^2 \, pq_U, \qquad (13)$$

where |U| denotes the number of elements in U and the sum is over all sets of distinct elements of size $k$, with only one permutation of each such set considered.

For diploids, we have the standard decomposition

$$V_G = V_A + V_D + V_{AA} + V_{AD} + V_{DD} + V_{AAA} + V_{AAD} + \ldots \qquad (14)$$

In this case, several coefficients contribute to each variance component. For instance, $V_A = \sum_{i \in Z} (b_{i_m}^2 + b_{i_f}^2) \, pq_i$. If we assume that *cis* and *trans* combinations have identical effects and that allelic effects do not depend on parental origin, then coefficients such as

$b_{i_m j_m}$, $b_{i_m j_f}$, $b_{i_f j_m}$ and $b_{i_f j_f}$ are identical. With this simplification and our convention about not treating permutations of indices separately, we have, as explained in Appendix 1,

$$V_A = 2\sum_{i\in Z} b^2_{i_m}\, p_i\, q_i, \quad V_{AA} = 4\sum_{\substack{i,j\in\mathbb{Z}\\ i<j}} b^2_{i_m j_m}\, pq_{ij},$$

$$V_D = \sum_{i\in Z} b^2_{i_m i_f}\, pq_i^2, \; V_{DD} = \sum_{\substack{i,j\in\mathbb{Z}\\ i<j}} b^2_{i_m i_f j_m j_f}\, pq_{ij}^2, \text{ and} \qquad (15)$$

$$V_{AD} = 2\sum_{\substack{i,j\in\mathbb{Z}\\ i<j}} b^2_{i_m i_f j_m}\, pq_i^2\, pq_j.$$

The powers of two arise from pooling coefficients that are identical under the assumption that *cis* and *trans* combinations are equivalent (see Eq. 16 below for further explanation).

To see the general pattern, consider the variance associated with additive effects at $k$ loci and dominance effects at $l$ loci, denoted $V_{A(k)\,D(l)}$. This involves summing over sets $\mathbb{S}$ involving $k+2l$ distinct positions where $k$ involve either the maternally or paternally inherited genes at distinct loci and the remaining $2l$ involve both the maternally and paternally inherited genes at $l$ other loci. Let $\mathbb{S}(k,l)$ denote a set of positions involving only the paternally derived genes from $k$ loci and both the paternally and maternally derived genes at $l$ other loci (with all $k+l$ loci distinct), and let $S_a(k)$ and $S_d(l)$ denote the sets of loci producing the additive and dominance contributions in $\mathbb{S}(k,l)$. The general form of the expressions in Eq. 15 is

$$V_{A(k)\,D(l)} = 2^k \sum_{\mathbb{S}(k,l)} b^2_{\mathbb{S}(k,l)}\, pq_{S_a(k)}\, (pq_{S_d(l)})^2, \qquad (16)$$

where the sum is over all sets of the form $\mathbb{S}(k,l)$ described above and only one permutation of each such set is considered. The leading term $2^k$ arises because either the paternally or maternally derived gene could be considered at the $k$ loci contributing additive terms to the interaction. Using the natural ordering, the first $\mathbb{S}(k,l)$ in this sum would be $\{1_m,\ 2_m, \ldots, k_m,\ (k+1)_m, (k+1)_f,\ \ldots (k+l)_f\}$.

## Changes in allele frequency

- **Changes in mean and genetic variance**

We consider next how the variance components change with allele frequencies. Suppose the allele frequencies change to $p_i^* = p_i + \Delta p_i$. This produces a new set of coefficients, $b_{\mathbb{U}}^*$, given by Eq. 3, that define the relation between genotype and phenotype with respect to the new reference point, $p_i^*$. The old deviation $\zeta_i = X_i - p_i$ can be rewritten as $\zeta_i = \zeta_i^* + \Delta p_i$. Taking the expectation of Eq. 2 over a population with allele frequencies $p_i^* = p_i + \Delta p_i$, we see that the change in trait mean is just

$$\Delta \bar{z} = \sum_{\mathbb{U} \neq \varnothing} b_{\mathbb{U}} \Delta p_{\mathbb{U}} . \qquad (17)$$

(To see this, note that the only non-zero terms in the expectation of Eq. 2 are those with $\mathbb{S} = \emptyset$ and $\mathbb{T} = \mathbb{U}$.) This expression applies to both haploids and diploids; in the latter case, the sets of positions $\mathbb{U}$ may include two elements from the same locus ($i_m$, $i_f$ say). We next consider how the total genetic variance changes. If the new population is at linkage equilibrium,

$$V_G^* = \sum_{\mathbb{U} \neq \varnothing} b_{\mathbb{U}}^{*2} pq_{\mathbb{U}}^* = \sum_{\mathbb{U} \neq \varnothing} b_{\mathbb{U}}^{*2} [pq - \Delta p\,(p - q) - \Delta p^2]_{\mathbb{U}} . \qquad (18)$$

To make further progress, we must specify the distribution of allele frequency fluctuations, $\Delta p$.

- **Effects of random drift on allele frequencies**

Suppose now that the changes in allele frequency are generated by random drift, with net identity coefficient $F$ describing the expected loss of heterozygosity at each locus. We will denote the expectation over the random fluctuations in allele frequency by $\langle\ \rangle$ to distinguish it from the expectation over the genotypes within a population (denoted $E[\ ]$). In general, we have

$$\langle \Delta p_i \rangle = 0, \quad \langle (\Delta p_i)^2 \rangle = F pq_i, \text{ and } \langle p_i^* q_i^* \rangle = (1 - F)\, pq_i . \qquad (19)$$

As discussed below, we will also show that our diffusion approximation implies

$$\langle \Delta p_{\mathbb{U}} \rangle = 0 \qquad (20)$$

for all sets $\mathbb{U}$ in which only one index appears for any locus (i.e., expectations are non-zero

only if all loci included in $\mathbb{U}$ appear at least twice). This implies that $\langle \Delta \bar{z} \rangle = 0$ for haploids. In general, the expectation of the squared trait mean is

$$\langle (\Delta \bar{z})^2 \rangle = \sum_{\mathbb{U} \neq \varnothing} \sum_{\mathbb{V} \neq \varnothing} b_{\mathbb{U}} \, b_{\mathbb{V}} \, \langle \Delta p_{\mathbb{U}} \, \Delta p_{\mathbb{V}} \rangle . \qquad (21)$$

This expectation depends on moments of the multivariate allele frequency distribution within and among loci. If the diffusion approximation applies, then the distribution of changes of allele frequencies at each locus is determined by the single parameter, $F$. However, distributions at different loci may not be statistically independent if recombination and drift occur at similar rates. This is because transient linkage disequilibria cause correlations between the magnitudes of changes at different loci. For example, even if the initial and final populations are at linkage equilibrium, there will be a correlation between $\langle \Delta p_i^2 \rangle$ and $\langle \Delta p_j^2 \rangle$. Moreover, the extent of these correlations will depend on the detailed pattern of population size during the bottleneck, rather than on the single parameter $F$. In Appendix 2, we give a general expression for the moments of the multilocus allele frequency distribution, assuming a constant rate of inbreeding (relative to recombination). Correlations between loci are strongest when drift is faster than recombination, and at intermediate levels of inbreeding ($2Nr \lesssim \frac{1}{2}$, $F \sim \frac{1}{4}$ to $\frac{1}{2}$), but even then, associations between pairs of loci are weak: the ratio $\frac{\langle \Delta p_i^2 \, \Delta p_j^2 \rangle}{\langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle}$ is never more than 1.13 (Fig. 1). The analogous ratio can be larger for three or four loci (maximum 1.46, 2.13 respectively, Fig. 2), and so it is possible that associations among large numbers of loci could have substantial cumulative effects on higher-order variance components, provided that linkage is tight relative to the rate of drift. However, in the following we will ignore such effects of linkage disequilibrium, and assume statistical independence across loci. In particular we assume that

$$\langle (\Delta p_i)^2 \, (\Delta p_j)^2 \rangle = F^2 pq_{ij}. \qquad (22)$$

We present below numerical results based on full multilocus dynamics that support this approximation.

## ■ Haploids

### ▪ Changes in mean

For haploids, Eq. 21 simplifies drastically. With statistical independence across loci, $\langle \Delta p_{\mathrm{U}} \, \Delta p_{\mathrm{V}} \rangle \neq 0$ only when U = V. Thus,

$$\mathrm{Var}(\bar{z}) = \langle (\Delta \bar{z})^2 \rangle = \sum_{U \neq \varnothing} b_U^2 \, F^{|U|} \, pq_U = \sum_{k=1}^{n} F^k \, V_{A(k)} , \tag{23}$$

where the last step follows from Eq. 13. Remarkably, for arbitrary epistasis, the variance in mean depends only on the variance components in the base population. Unless $F$ is large, higher-order epistasis makes a small contribution. Nevertheless, nonadditive components do contribute: in the limit $F = 1$, a random genotype is fixed, and so necessarily the variance of population means is equal to the variance of genotypic values, $V_G = \sum_{k=1}^{n} V_{A(k)}$.

As a concrete example, consider the following two-locus haploid model: $\begin{pmatrix} 1+\epsilon & 1 \\ 1 & 1+\epsilon \end{pmatrix}$. In terms of indicator variables $X_1$ and $X_2$, the genotypic value of $(X_1, X_2)$ is $1 + \epsilon[X_1 X_2 + (1 - X_1)(1 - X_2)]$. For this model, $b_1 = \epsilon(p_2 - q_2)$, $b_2 = \epsilon(p_1 - q_1)$, and $b_{12} = 2\epsilon$. At LE, the mean is $1 + \epsilon(p_1 p_2 + q_1 q_2)$, and so the change in mean at LE is $\epsilon((p_1 - q_1)\Delta p_2 + (p_2 - q_2)\Delta p_1 + 2\Delta p_1 \Delta p_2)$. With independent changes across loci, $\langle \Delta \bar{z}^2 \rangle = \epsilon^2 [F(p_1 - q_1)^2 pq_2 + F(p_2 - q_2)^2 pq_1 + 4F^2 pq_{12}]$. The first two terms equal $F V_A$, and the last term equals $F^2 V_{AA}$.

- **Changes in variance**

The expected genotypic variance is given in a similar way

$$\begin{aligned} \langle V_G^* \rangle &= \left\langle \sum_{U \neq \emptyset} \left( \sum_{V \subseteq Z \setminus U} b_{UV} \, \Delta p_V \right)^2 pq_U^* \right\rangle \\ &= \sum_{U \neq \emptyset} (1 - F)^{|U|} \, pq_U \sum_{V \subseteq Z \setminus U} b_{UV}^2 \, \langle (\Delta p_V)^2 \rangle \\ &= \sum_{U \neq \emptyset} (1 - F)^{|U|} \sum_{V \subseteq Z \setminus U} F^{|V|} \, b_{UV}^2 \, pq_{UV} . \end{aligned} \tag{24}$$

This follows because $\langle \Delta p_V \, \Delta p_W \rangle = 0$ unless V = W. Summing over all sets UV = W, then partitioning the W by size, we can rewrite this as

$$\langle V_G^* \rangle = \sum_{W \neq \emptyset} b_W^2 \, pq_W \sum_{\substack{UV=W \\ U \cap V = \emptyset \\ U \neq \emptyset}} (1-F)^{|U|} F^{|V|}$$

$$= \sum_{k=1}^{n} \sum_{|W|=k} b_W^2 \, pq_W \sum_{\substack{UV=W \\ U \cap V = \emptyset \\ U \neq \emptyset}} (1-F)^{|U|} F^{|V|} \qquad (25)$$

$$= \sum_{k=1}^{n} V_{A(k)} \sum_{j=1}^{k} \binom{k}{j} [(1-F)^j F^{k-j}]$$

$$= \sum_{k} V_{A(k)} (1 - F^k) = V_G - \sum_{i=1}^{n} F^k V_{A(k)},$$

where the binomial coefficient arises from the number of ways in which sets W of size $k$ can be partitioned into the components U ($\neq \emptyset$) and V. We are now expressing the new total genotypic variance as a sum over the original variance components. We see that the original additive variance is deflated by $1 - F$, but the higher-order components contribute relatively more of their initial values to the final expected genetic variance. (For example, $V_{A(2)}$ contributes a fraction $1 - F^2$ of its initial value to $\langle V_G^* \rangle$ while $V_A$ contributes only $1 - F$.)

Next we consider the individual components of variance. Splitting $\langle V_G^* \rangle$ into components, we have for |U| = j,

$$\langle V_{A(j)}^* \rangle = (1-F)^j \sum_{|U|=j} \sum_{V \subseteq Z \setminus U} F^{|V|} \, b_{UV}^2 \, pq_{UV}. \qquad (26)$$

Proceeding as in our derivation of $\langle V_G^* \rangle$, we can write

$$\langle V_{A(j)}^* \rangle = (1-F)^j \sum_{|W| \geq j} \binom{|W|}{j} F^{|W|-j} \, b_W^2 \, pq_W, \qquad (27)$$

where the binomial coefficient counts the number of ways in which a specific set W can arise from different sets U and V. Collecting the terms corresponding to specific values of |W|, we see that

$$\langle V^*_{A\,(j)} \rangle = (1 - F)^j \sum_{k=0}^{n-j} \binom{k+j}{j} F^k V_{A\,(j+k)} \,. \qquad (28)$$

It is easy to see that summing Eq. 28 over $j$ reproduces Eq. 25. This expression provides some justification for the idea that drift "converts" higher-order epistatic variances into lower-order variance components. (For instance, $V_{AAA}$ contributes to both $\langle V^*_A \rangle$ and $\langle V^*_{AA} \rangle$). However, note that this direct relationship applies only in expectation, and only in the absence of dominance.

Figure 3 shows how the variance components change under drift with an extreme model of epistasis, for a haploid population with 5 loci. Genotypic values were drawn randomly from a normal distribution with variance 1 (see Appendix 3). Throughout, most genetic variance is additive (upper heavy curves); this increases slightly with drift up to a maximum at $F \sim 0.5$, while higher-order epistatic components decline (lower curves). The predictions from Eq. 28 (dashed curves) agree well with the averages over 100 simulations. This provides a check on our assumption that allele frequencies fluctuate independently, despite transient linkage disequilibria. However, as illustrated below, individual simulations are typically well away from the expectation shown in Fig. 3.

For $j = 1$, Eq. 28 shows that

$$\langle V^*_A \rangle = (1 - F)\,(V_A + 2\,F\,V_{AA} + 3\,F^2\,V_{AAA} + \ldots) \,. \qquad (29)$$

Thus epistasis always inflates $\langle V^*_A \rangle$ above the value, $V_A(1 - F)$, expected with additivity. Similarly, Eq. 28 shows that the expected value of *every* component of variance is inflated by contributions from higher-order epistatic components. Eq. 25 shows that drift erodes higher-order variance components more slowly than lower-order components, and Eq. 28 shows that these higher-order components contribute to the expected post-bottleneck values of all lower-order components. This interaction of drift and epistasis remains true with diploidy, but its effects are confounded by dominance, which as discussed below can either increase or decrease $\langle V^*_A \rangle$ from the additive expectation.

Although some effort is required to get the exact expression describing how epistasis inflates $\langle V^*_A \rangle$, our notation provides a simple way to understand the origin of this effect. Note that by definition

$$\langle V_A^* \rangle = \langle \sum_{i=1}^{n} (b_i^*)^2 \, (p_i^* \, q_i^*) \rangle$$

From Eq. 3, we see that $b_i^* = \sum_{\mathbb{V} \subseteq \mathbb{Z} \setminus i} b_{i\mathbb{V}} \, \Delta p_{\mathbb{V}} = b_i + \sum_{\emptyset \neq \mathbb{V} \subseteq \mathbb{Z} \setminus i} b_{i\mathbb{V}} \, \Delta p_{\mathbb{V}} \equiv b_i + \Delta b_i$ , where $\Delta b_i$ depends on changes in allele frequencies only at loci other than $i$. Hence, our approximation that changes in allele frequencies at disjunct loci are independent implies that $\langle \Delta b_i \rangle = 0$ and

$$\langle V_A^* \rangle = \langle \sum_{i=1}^{n} (b_i + \Delta b_i)^2 \, (p_i^* \, q_i^*) \rangle$$

$$= \sum_{i=1}^{n} b_i^2 \langle p_i^* \, q_i^* \rangle + \sum_{i=1}^{n} \langle (\Delta b_i)^2 \rangle \langle p_i^* \, q_i^* \rangle$$

$$> \sum_{i=1}^{n} b_i^2 \langle p_i^* \, q_i^* \rangle = (1 - F) \sum_{i=1}^{n} b_i^2 \, p_i \, q_i = V_A (1 - F).$$

Here we see explicitly how drift "converts" epistatic interactions into an expected increase in $V_A$. This conversion depends critically on $\langle \Delta b_i \rangle = 0$ and the independence of $\Delta b_i$ and $p_i^* \, q_i^*$. A similar inequality (and derivation) holds for all components of variance, the expected value of each is inflated by contributions from higher-order variance components. In contrast, these inequalities do not hold with dominance, because $\langle \Delta b_i \rangle \neq 0$ and $\Delta b_i$ and $p_i^* \, q_i^*$ are not independent.

Eq. 29 shows that $V_A$ increases on average, i.e., $\langle V_A^* \rangle > V_A$, only if

$$V_A < (1 - F) \, (2 \, V_{AA} + 3 \, F V_{AAA} + 4 \, F^2 \, V_{A(4)} + \ldots) . \qquad (30)$$

For small F, this reduces to $V_A < 2 \, V_{AA}$. For any $F \leq 2/3$, a necessary condition for $V_A$ to increase on average is that

$$2 \, (V_G - V_A) > V_A \quad \text{or} \quad \frac{V_A}{V_G} < \frac{2}{3} . \qquad (31)$$

Thus, although epistasis always inflates $\langle V_A^* \rangle$, additive variance can actually increase on average only if the epistatic components constitute at least one-third of the total genetic variance.

From Eq. 29 and Eqs. 23 and 25 we see that there is a simple relation between the variance in mean and the expected *new* additive variance:

$$\langle (\Delta \bar{z})^2 \rangle \leq \frac{F}{1 - F} \langle V_A^* \rangle , \qquad (32)$$

with equality in general only if there is no epistatic variance. However, approximate equality holds if epistatic components are relatively small. For low levels of inbreeding, $\langle(\Delta \bar{z})^2\rangle \cong F \langle V_A^* \rangle$, implying that the variance in the change of the mean is proportional to the *new* additive variance, averaged over realizations. Thus, even if the initial population has no additive variance, the mean may still change as a result of nonadditive components. This change, however, is proportional to the expected additive variance generated by drift. Note that this relation is between expectations over many realizations. The correlation between $\Delta \bar{z}$ and $V_A^*$ in any *particular* realization may be weak. For the model discussed below in which diploid genotypic values are chosen at random (to produce extreme epistasis), we found that this correlation declines from ~0.5 for small F to near zero for strong inbreeding (results not shown).

## ■ Diploids

### ▪ Changes in mean

In diploids, even when the changes across loci are independent, the expected change in mean may be non-zero because of dominance. To understand these effects, it is useful to distinguish coefficients $b_{\mathbb{U}}$ in which positions corresponding to both paternally and maternally acting alleles at a locus appear. For each set $\mathbb{U}$ that includes only distinct positions, we can write

$$\mathbb{U} = A \mid B, \tag{33}$$

where A and B do not overlap, A contains the indices for the loci that appear only once in $\mathbb{U}$, and B contains the loci that appear as both $i_m$ and $i_f$. For instance, in this notation, $b_{\{i_m,i_f\}} \equiv b_{\emptyset|\{i\}}$. Because $\langle \Delta p_i \rangle = 0$ and the fluctuations are assumed to be independent, only sets $\mathbb{U}$ in which all loci belong to B contribute nonzero terms to $\langle \Delta \bar{z} \rangle$. Assuming statistically independent loci, the expected change in mean is

$$\langle \Delta \bar{z} \rangle = \sum_{\mathbb{U} \neq \emptyset} b_{\mathbb{U}} \langle \Delta p_{\mathbb{U}} \rangle = \sum_{V \neq \emptyset} b_{\emptyset \mid V} F^{|V|} pq_V, \tag{34}$$

where the sum is over all nonempty sets V of distinct loci. Note that the mean changes only through pure dominance components, $b_{\emptyset \mid V}$, because only then do terms $\Delta p_i^2$ appear in the product $\Delta p_{\mathbb{U}}$. The coefficient $b_{\{i_m,i_f\}} \equiv b_{\emptyset|\{i\}}$ is negative if recessive alleles tend to reduce the trait (see the example described in Eq. 46 below). Similarly, $b_{\{i_m,i_f,j_m,j_f\}} \equiv b_{\emptyset|\{i,j\}}$ is negative if two recessive alleles at loci $i$ and $j$, or two dominant alleles, tend to reduce the trait, and so on

for higher-order terms. It is the sign of these pure dominance coefficients that determines whether the trait will decrease as a result of drift — that is, whether there will be inbreeding depression.

Next, consider the variance of the trait mean, var($\Delta\bar{z}$). This is given by subtracting the square of the mean (Eq. 34) from the mean square (Eq. 21). Because a locus $i$ can now appear up to four times in the expectation $\langle \Delta p_U \, \Delta p_V \rangle$ that appears in Eq. 21, we must consider third- and fourth-order moments. Before treating this complication, we first consider the much simpler case in which there are no dominance effects. In this case, $\langle \Delta\bar{z} \rangle = 0$. Moreover, because $b_{A|B} = 0$ if $B \neq \emptyset$, we need consider only terms in Eq. 21 that involve at most one position from each locus. Thus, we can replace the sum in Eq. 21 over positions with a sum over loci, but terms corresponding to sets of $k$ loci must be multiplied by $2^k$ to account for the fact that either paternally or maternally inherited alleles could have been chosen at each locus. Hence, Eq. 21 becomes

$$\mathrm{Var}(\bar{z}) = \langle (\Delta\bar{z})^2 \rangle = \sum_{U \neq \emptyset} \sum_{V \neq \emptyset} 2^{|U|+|V|} \, b_U \, b_V \, \langle \Delta p_U \, \Delta p_V \rangle . \tag{35}$$

As in the haploid case, our assumption that changes are independent across loci implies that $\langle \Delta p_U \, \Delta p_V \rangle = 0$ if $U \neq V$, whereas $\langle (\Delta p_U)^2 \rangle = F^{|U|} \, pq_U$. Applying this simplification and the definition of $V_{A(k)}$ for diploids, we see that

$$\begin{aligned} \mathrm{Var}(\bar{z}) = \langle (\Delta\bar{z})^2 \rangle &= \sum_{U \neq \emptyset} (2F)^{|U|} \, 2^{|U|} \, b_U^2 \, pq_U \\ &= \sum_{k=1}^{n} (2F)^k \, V_{A(k)} . \end{aligned} \tag{36}$$

This differs from the haploid case only by the appearance of $2F$ rather than $F$, and it serves as a simple check for the more complex calculation below with dominance.

With dominance, we need approximations for $\langle \Delta p_i^k \rangle$ up to $k = 4$. From 7.4.32 and 7.4.33 of Crow and Kimura (1970),

$$\begin{aligned} &\langle \Delta p_i^2 \rangle = F \, pq_i , \\ &\langle \Delta p_i^3 \rangle = \frac{F^2}{2} (3 - F) \, pq_i \, (q_i - p_i) , \text{ and} \\ &\langle \Delta p_i^4 \rangle = \frac{F^2}{5} \, pq_i \, (A + B \, pq_i) \\ &\text{where } A = F \, [15 \, (1 - F) + 6 F^2 - F^3] , \text{ and} \end{aligned} \tag{37}$$

$$B = 5\,(3 - 16F + 15F^2 - 6F^3 + F^4) = 5\,(3 - F - A).$$

Because $\langle \Delta p_i^3 \rangle$ and $\langle \Delta p_i^4 \rangle$ are not proportional to the $pq_i$, $\langle (\Delta \bar{z})^2 \rangle$ cannot be expressed solely in terms of variance components, which depend only on sums of terms of the form $pq_U$ (see Eq. 16). (The complication would also arise in the haploid case if we had not assumed statistical independence across loci: then, $\langle \Delta p_i^2 \, \Delta p_j^2 \rangle$ would contribute complicating terms in the same way that $\langle \Delta p_i^3 \rangle$ and $\langle \Delta p_i^4 \rangle$ do here.) The leading terms in the expression for the variance in trait mean, obtained by substituting for allele frequency moments from Eq. 37, are given in Appendix 4.

Assembling the pieces from Appendix 4, and writing terms that involve sums of the form $\sum_{\mathbb{U}} b_{\mathbb{U}}^2 \, pq_{\mathbb{U}}$ as variance components, we obtain

$$\begin{aligned}
&\mathrm{var}\,(\Delta \bar{z}) = 2FV_A - F^2 V_D + 4F^2 V_{AA} - F^4 V_{DD} + \\
&\quad + \tfrac{F^2}{5} V_D \left\{ \tfrac{A}{pq} + B \right\}_D + \tfrac{4F^3}{5} V_{AD} \left\{ \tfrac{A}{pq} + B \right\}_{AD} \\
&+ \tfrac{F^4}{25} V_{DD} \left\{ \left( \tfrac{A}{pq} + B \right)^2 \right\}_{DD} \\
&+ 2F^2 (3 - F) \textstyle\sum_i b_{\{i\}|\emptyset} \, b_{\emptyset|\{i\}} \, pq_i \, (q_i - p_i) \\
&+ F^2 \textstyle\sum_{i \neq j} (8 \, b_{\{i\}|\emptyset} \, b_{\{i\}|\{j\}} - b_{\emptyset|\{i\}} \, b_{\emptyset|\{j\}}) \, pq_{ij} \\
&+ 2F^3 (3 - F) \\
&\quad \textstyle\sum_{i \neq j} (4 \, b_{\{i,j\}|\emptyset} \, b_{\{j\}|\{i\}} + b_{\emptyset|\{i\}} \, b_{\{i\}|\{j\}} + b_{\{i\}|\emptyset} \, b_{\emptyset|\{i,j\}}) \\
&\qquad (q_i - p_i) \, pq_{ij} \\
&+ F^4 (3 - F)^2 \textstyle\sum_{i \neq j} (b_{\{i,j\}|\emptyset} \, b_{\emptyset|\{i,j\}} + b_{\{i\}|\{j\}} \, b_{\{j\}|\{i\}}) \\
&\qquad (q_i - p_i)(q_j - p_j) \, pq_{ij} \\
&+ \tfrac{2F^3}{5} \textstyle\sum_{i \neq j} b_{\emptyset|\{i\}} \, b_{\emptyset|\{i,j\}} \, pq_{ij} \, (A + (B - 5) \, pq_i) \\
&+ \tfrac{2F^4}{5} (3 - F) \\
&\qquad \textstyle\sum_{i \neq j} b_{\{i\}|\{j\}} \, b_{\emptyset|\{i,j\}} \, (q_i - p_i) \, pq_{ij} \, (A + B pq_j) + \ldots
\end{aligned} \tag{38}$$

where $\left\{ \tfrac{A}{pq} + B \right\}_D$ indicates an average across loci, weighted by contributions to the dominance component (e.g., $\sum_i b_{\emptyset|\{i\}}^2 \, pq_i = V_D \left\{ \tfrac{1}{pq} \right\}_D$). Similar definitions apply to other variance components, with $V_{DD} \left\{ \left( \tfrac{A}{pq} + B \right)^2 \right\}_{DD}$, for instance, a shorthand for an average involving products of terms in which two different loci appear (see Appendix 4 for the full expressions). There are two reasons why the variance in trait mean does not depend solely on variance components. First, as shown by Eq. 16, variance components depend on allele frequencies only through products of the form $pq_{\mathbb{U}}$, whereas higher moments such as $\Delta p_i^3$ and $\Delta p_i^4$ do not depend solely on $pq_i$. This leads to weighted averages of allele frequency, such as

$\frac{F^2}{5} V_D \left[ \frac{A}{pq} + B \right]_D$ above. Second, and more seriously, Eq. 38 includes many cross-terms, such as $b_{\{i\}|\emptyset} b_{\emptyset|\{i\}}$, that can be interpreted as weighted covariances between different sorts of effects (e.g., covariances between additive effects and dominance interactions). Such terms cannot be expressed in terms of variance components.

Equation 38, like Eq. 36, shows that the additive variance components contribute to changes in the mean in the same way as in the haploid case, except that the contribution of $V_{A(k)}$ is inflated by $2^k$. There is also a contribution from the dominance variance, which may be relatively large if rare alleles are involved (i.e. if $pq << 1$, so that $\left[ \frac{A}{pq} + B \right]_D$ is large). However, the dominance variance itself cannot be large in that case, because it is proportional to the *squared* heterozygosity at each locus. The complications attributable to dominance are elaborated below when we discuss its effects on expected changes in additive variance.

Figure 4 shows a numerical example using the model of randomly chosen diploid genotypic values discussed in Appendix 3. This model generates extreme epistasis. We assume complete dominance at each locus, with homozygous phenotypes chosen randomly from a Gaussian with mean zero and variance one. Allele frequencies in the base population were intermediate (see figure legend), which allows a relatively high proportion of nonadditive variance (initially, $V_A = 0.40$ and $V_G = 1.16$). The variance in the change of the mean, averaged over 1000 replicates, is close to that predicted by Eq. 38. Part of the discrepancy is due to deviations of the distribution of allele frequencies from the expected values (Eq. 37). If the actual moments, calculated from the 1000 replicates, are used, the fit is closer (Fig. 4). The remaining discrepancy arises from chance correlations between fluctuations at different loci. As shown in Appendix 2, the effects of these correlations, which are ignored in our approximations, are very slight, unless $F$ is extremely large.

The first term in Eq. 38 is $2FV_A$, and so dominates for small $F$ (straight line in Fig. 4). For large $F$, however, the variance in mean is greater than predicted by this leading term, because of contributions from the nonadditive terms. These contributions are shown separately in Fig. 5, which shows both positive and negative terms. Table 2 shows the terms that make the largest contributions. Note, however, that at least for $F < 0.5$, these additional contributions are never large, and the fluctuations of the trait mean are predicted well from $V_A$ in the base population.

■ **Changes in variance**

We first obtain the expected values of the total genetic variance and the individual additive components assuming no dominance. This yields simple diploid analogs of our haploid results. We then find the expected additive variance in the general case with dominance.

Using the general expression for $V_G$, and substituting for the new $b_{\mathbb{U}}$ from Eq. 3, we obtain:

$$\begin{aligned}\langle V_G^* \rangle &= \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} \left\langle (b_{\mathbb{U}}^*)^2 \, pq_{\mathbb{U}}^* \right\rangle \\ &= \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} \sum_{\mathbb{V},\mathbb{W} \subseteq \mathbb{Z} \setminus \mathbb{U}} b_{\mathbb{U}\mathbb{V}} \, b_{\mathbb{U}\mathbb{W}} \langle \Delta p_{\mathbb{V}} \, \Delta p_{\mathbb{W}} \, pq_{\mathbb{U}}^* \rangle \\ &= \sum_{\emptyset \neq \mathbb{U} \subseteq \mathbb{Z}} \sum_{\mathbb{V},\mathbb{W} \subseteq \mathbb{Z} \setminus \mathbb{U}} b_{\mathbb{U}\mathbb{V}} \, b_{\mathbb{U}\mathbb{W}} \langle \Delta p_{\mathbb{V}} \, \Delta p_{\mathbb{W}} \, pq_{\mathbb{U}}^* \rangle .\end{aligned} \qquad (39)$$

Assuming no dominance, $b_{\mathbb{U}\mathbb{V}} \, b_{\mathbb{U}\mathbb{W}} = 0$ unless each set $\mathbb{U}$, $\mathbb{V}$, $\mathbb{W}$ contains each locus at most once. For all of the remaining sets, in which each locus appears at most once, there are $2^k$ ways in which a set of $k$ positions can be allocated to the maternal or paternal genomes. Allowing for this factor, we can sum over all sets of loci, rather than all sets of positions (i.e., our reference now is as in the haploid case, Z = {1, 2, ... n}). This yields

$$\langle V_G^* \rangle = \sum_{\emptyset \neq U \subseteq Z} \sum_{V,W \subseteq Z \setminus U} 2^{|UVW|} \, b_{UV} \, b_{UW} \langle \Delta p_V \, \Delta p_W \, pq_U^* \rangle , \qquad (40)$$

where now $b_{UV}$ refers to one of the $2^{|UV|}$ sets of coefficients $b_{\mathbb{U}\mathbb{V}}$ involving the set of loci $UV$. Because U is disjunct from V and W, our independence assumption implies that $\langle \Delta p_V \, \Delta p_W \, pq_U^* \rangle = \langle \Delta p_V \, \Delta p_W \rangle \langle pq_U^* \rangle$. Similarly, the expectation over allele frequency changes is nonzero only when V = W. Substituting for the allele frequency moments in terms of $F$,

$$\begin{aligned}\langle V_G^* \rangle &= \sum_{\emptyset \neq U \subseteq Z} \sum_{V \subseteq Z \setminus U} 2^{|UVV|} \, b_{UV}^2 \langle (\Delta p_V)^2 \rangle \langle pq_U^* \rangle \\ &= \sum_{\emptyset \neq U \subseteq Z} \sum_{V \subseteq Z \setminus U} 2^{|UV|} \, b_{UV}^2 \, pq_{UV} \, (1 - F)^{|U|} \, (2F)^{|V|} .\end{aligned} \qquad (41)$$

Following our calculation in the haploid case, we rearrange the sum to run over sets $UV = W$, partition this sum into terms ordered by |W|, and use the additive, diploid expression $V_{A(k)} = 2^k \sum_{|U|=k} b_U^2 \, pq_U$, to obtain

$$\begin{aligned}
\langle V_G^* \rangle &= \sum_{\emptyset \neq W} 2^{|W|} \, b_W^2 \, pq_W \sum_{\substack{UV=W \\ U \cap V = \emptyset \\ U \neq \emptyset}} (1-F)^{|U|} \, (2F)^{|V|} \\
&= \sum_{k=1}^{n} V_{A(k)} \sum_{j=1}^{k} \binom{k}{j} \left[ (1-F)^j \, (2F)^{k-j} \right] \qquad (42) \\
&= \sum_{k=1}^{n} \left[ (1+F)^k - (2F)^k \right] V_{A(k)} \, .
\end{aligned}$$

(This agrees with the expression given in Walsh and Lynch 1998, Ch. 3.) As in the haploid case, the binomial coefficient arises from the number of combinations of V and non-empty U that can produce a specific set W. As expected, the contribution from the additive variance (k=1) is $(1 - F) \, V_A$.

Next we consider the expected values for the individual components of additive variance without dominance. Following the derivations above, we have

$$\begin{aligned}
\langle V_{A(j)}^* \rangle &= (1-F)^j \sum_{|U|=j} \sum_{V \subseteq Z \setminus U} 2^{|UV|} \, b_{UV}^2 \, pq_{UV} \, (2F)^{|V|} \\
&= (1-F)^j \sum_{|W| \geq j} \binom{|W|}{j} 2^{|W|} \, b_W^2 \, pq_W \, (2F)^{|W|-j} \qquad (43) \\
&= (1-F)^j \sum_{k=0}^{n-j} \binom{k+j}{j} (2F)^k \, V_{A(j+k)} \, .
\end{aligned}$$

This differs from the haploid result (Eq. 28) only in that $2F$ replaces $F$. In particular, the expected additive variance is

$$\langle V_A^* \rangle = (1-F) \sum_{k=0}^{n-1} (k+1) \, (2F)^k \, V_{A(k+1)} \; > \; (1-F) \, V_A \, . \qquad (44)$$

Thus, just as in the haploid case, epistatic interactions, in the absence of dominance, always inflate the expected additive variance after a bottleneck above that expected with purely additive allelic effects. Equation 44 also shows that we expect the additive variance to increase on average with small $F$ only if

$$4\,V_{AA} > V_A. \tag{45}$$

In Appendix 4, we derive the expected additive genetic variance after the bottleneck for the general case with dominance. As found for the variance of the mean, the expected change in additive variance cannot be expressed in terms of variance components in the base population: the outcome depends on weighted variances and covariances among different kinds of effects. Before discussing the general expression, we first consider dominance in the absence of interactions across loci: as illustrated by the simple expressions derived with "pure" epistasis, dominance is the source of the complications. Suppose that the genotypic value is determined by additive contributions from $n$ loci with dominance within each locus described as follows:

$$\begin{aligned} z &= \sum_{i=1}^{n} g_i, \text{ with} \\ g_i\,(X_{i_f}, X_{i_m}) &= a_i\,X_{i_f}\,X_{i_m} + \\ &\quad d_i\,[X_{i_m}\,(1 - X_{i_f}) + X_{i_f}\,(1 - X_{i_m})] - a_i\,(1 - X_{i_f})\,(1 - X_{i_m}), \end{aligned} \tag{46}$$

so that homozygosity for allele 1 (0) at locus $i$ contributes $a_i$ ($-a_i$) to $z$ and the heterozygosity contributes $d_i$. Thus, if $d_i \equiv 0$ we have pure additivity. Under Eq. 46, the only non-zero $b_{\mathbb{U}}$ are

$$\begin{aligned} b_{i_m} &= b_{i_f} = a_i + (q_i - p_i)\,d_i \text{ and} \\ b_{i_f\,i_m} &\equiv b_{\emptyset|\{i\}} = d_i. \end{aligned} \tag{47}$$

In this case, the general expression in Appendix 4 reduces to

$$\begin{aligned} \langle V_A^* \rangle = (1 - F) \Bigg( & V_A + 2\,FV_D + \frac{F}{5}\,V_D\,(D - 10) + 2\,F\,(2 - F) \\ & \sum_i pq_i\,b_{i_m i_f}\,b_{i_m}\,(q_i - p_i) + \frac{F}{5}\,V_D \left[\frac{C}{pq_i}\right]_D \Bigg), \end{aligned} \tag{48}$$

where $C = F\,(15 - 20\,F + 10\,F^2 - 2\,F^3) \geq 0$ and
$D = 10\,(1 - 8\,F + 10\,F^2 - 5\,F^3 + F^4)$. The first term is the standard additive result. The

second term is a positive contribution from dominance variance; but the third term, which involves higher powers of $F$, is always negative. The fourth and fifth terms cannot be expressed in terms of variance components. The fifth term is always positive, but it is proportional to $F^2$ for small $F$. The fourth term can be thought of as a weighted covariance between the additive and dominance effects at each locus. If the 1 alleles are rare ($p_i << 1$), this term will be positive if these alleles tend to be recessive (i.e., $b_{i_f\, i_m} = d_i < 0$) but negative if they are generally partially dominant ($d_i > 0$). Note that if the 1 alleles are all rare and $F$ is small, this "covariance" term dominates the deviation from the additive prediction (because it depends on $p_i$, whereas dominance variance depends on $p_i^2$). Thus, unlike pure epistasis, dominance can either increase or decrease the expected additive variance. The fact that drift can inflate additive variance with rare recessive alleles was first noted by Robertson (1952) and elaborated by Willis and Orr (1993) as a possible explanation of the experimental results of Bryant et al. (1986).

In Appendix 4, we show that in general

$$
\begin{aligned}
\langle V_A^* \rangle = \\
(1-F)\Bigg( & V_A + 2FV_D + \frac{F}{5} V_D \left[ \frac{C}{pq_i} + (D-10) \right]_D + 4F V_{AA} + \\
& 2\frac{F^2}{5} V_{AD} \left[ \frac{C}{pq_i} + D \right]_{AD} \\
& + 2F(2-F) \sum_i pq_i b_{i_m i_f} b_{i_m} (q_i - p_i) \\
& + 8F^2(2-F) \sum_{i \neq j} pq_{ij} (b_{i_m i_f j_m} b_{i_m j_m}) (q_i - p_i) \qquad (49) \\
& + 4F \sum_{i \neq j} pq_{ij} \Big( b_{i_m j_m j_f} b_{i_m} + \frac{F}{2}(2-F) \\
& \quad (b_{i_m i_f j_m j_f} b_{i_m} + b_{i_m j_m j_f} b_{i_m i_f})(q_i - p_i) + \\
& \quad \frac{F}{10}(C + D pq_i) b_{i_m i_F j_m j_F} b_{i_m i_F} \Big) + \cdots \Bigg),
\end{aligned}
$$

where C and D are as in Eq. 48. Thus, in diploids, because of the complications introduced by dominance, there is no simple relation between the expected components of genetic variance after drift and the variance components in the base population.

Figure 6 shows how the expected additive variance changes under drift, for the same genotypic values as in Fig. 4. The prediction from Eq. 49 fits with the average of 1000 replicate simulations. On average, $V_A$ increases up to $F \sim 0.3$, and is much greater than expected under additivity (straight line in Fig. 6). However, as shown in Fig. 7, there is a great deal of variation among individual realizations.

## ■ Slight inbreeding

Some insight can be gained by finding how the additive genetic variance changes as inbreeding increases from zero. That is, we consider $\partial_F \langle V_A^* \rangle$ at $F = 0$. The expressions then simplify drastically, because higher-order moments of allele frequency are proportional to $F^2$ (Eq. 37) and so can be neglected.

For haploids, differentiating Eq. 29 gives

$$\frac{\partial \langle V_A^* \rangle}{\partial F} = -V_A + 2\,V_{AA}. \qquad (50)$$

Thus, the additive genetic variance is expected to increase with drift if $2V_{AA} > V_A$.

For diploids, the leading terms in $F$ are all included in the terms shown in Eq. 49. Differentiating and setting $F$ to zero,

$$\frac{\partial \langle V_A^* \rangle}{\partial F} = -V_A + 2V_D + 4\,V_{AA} + 2\,C_{AD},$$
$$\text{where } C_{AD} = \qquad (51)$$
$$2\sum_i pq_i\,(q_i - p_i)\,b_{i_m i_f}\,b_{i_m} + 2\sum_{i\neq j} pq_{ij}\,b_{i_m j_m}\,b_{j_f i_m}.$$

Thus, dominance variance contributes to an increase in the additive genetic variance in the same way that additive×additive epistasis does. In contrast, there is no leading-order contribution from the higher-order variance components such as $V_{AAA}$ nor from pairwise components that involve dominance, such as $V_{AD}$ and $V_{DD}$. The last term, $C_{AD}$, in Eq. 51 is difficult to interpret. The first sum involves associations between dominance interactions and additive effects, while the second involves associations between additive-by-dominance interactions and additive effects. The first sum in $C_{AD}$, called $\sigma^2_{ADI}$ in Walsh and Lynch's (1998) discussion of Cockerham and Tachida (1988) (see Eqs. 74, 76 in Appendix 5), can be most easily interpreted if we think of the trait as a fitness component. The contribution of a locus to inbreeding depression is $b_{i_m i_f} pq_i$. For a fitness trait, we expect that inbreeding at the locus reduces the trait, so that $b_{i_m i_f} < 0$. Now, if $b_{i_m}$ is positive, then the '0' allele is

deleterious and we expect it to be rare (i.e. $q_i << p_i$). Hence, $(q_i - p_i)\, b_{i_m}$ is expected to be negative if the trait is under positive selection. On this argument, we expect the first contribution to $C_{\mathrm{AD}}$ to be positive if the trait is a fitness component which shows inbreeding depression. However, the term may still be positive even if there is no overall inbreeding depression. Suppose that alleles at each locus influence fitness, and also have a random pleiotropic effect on the trait. Then, we will on average see no inbreeding depression for the trait, but the first term in $C_{\mathrm{AD}}$ will nevertheless be positive.

The rate of change of $\langle V_A^* \rangle$ near $F = 0$ should be a good guide to whether inbreeding can, on average, increase the additive genetic variance. However, it is possible that higher-order terms will change the gradient, so that $\langle V_A^* \rangle > V_A$ for some intermediate $F$, even if $\partial_F \langle V_A^* \rangle < 0$ at $F = 0$. In the haploid case, for example, Eq. 29 shows that this would be the case if $2V_{\mathrm{AA}} < V_A$, but $V_{\mathrm{AAA}}$ were sufficiently large.

## Discussion

We have shown that for haploids, and for diploids without dominance, there is a simple relation between variance components in the base population and the variance of the trait mean and the expected values of variance components after a population bottleneck. With no dominance, therefore, the idea that drift "converts" nonadditive to additive variance makes sense: one can identify the contribution of each initial variance component to the expected value of each variance component after drift (Eq. 28). Without dominance, the expected value of every variance component is inflated by contributions from higher-order epistatic interactions (e.g., third-order interactions add to the expected value of $V_{\mathrm{AA}}$). However, dominance (even without epistasis) can reduce expected variances. For instance, the expected additive variance can fall below $V_A(1 - F)$, the value expected with purely additive allelic effects. Covariances among different kinds of effects contribute and no explicit formula for the additive variance after drift is possible in terms of variance components in the base population (see Eq. 49). Thus, it is generally misleading to think of "conversion" of nonadditive variance components into additive variance.

Our results generalize Cockerham and Tachida's (1988) two-locus analysis to arbitrarily many loci. Although our expressions include the terms that they identify (Appendix 5), we find extra contributions even for small $F$ and only two loci. In particular, the rate of change of expected additive variance with $F$ near 0 ($\partial_F \langle V_A^* \rangle$) includes Cockerham and Tachida's expression (1988, p. 1565), but has an extra term that arises from additive×dominance interactions (Eq. 51). Our derivation is more restrictive than Cockerham and Tachida's (1988)

because it assumes two alleles per locus, and because it neglects linkage disequilibrium throughout. We believe that our results can be extended to multiple alleles by using multilocus identity probabilities (defining $F_{\mathbb{U}}$ as the probability that alleles at positions in the set $\mathbb{U}$ are identical by descent). Our neglect of linkage disequilibrium is also unlikely to cause significant error. Linkage disequilibrium makes no significant contribution for slight inbreeding, and Tachida and Cockerham (1989) showed that with two loci, identity disequilibria (that is, correlations of identity-by-descent across loci) have negligible effects. We extend their analysis of identity disequilibria by showing that correlations between allele frequency fluctuations (e.g., $\langle \Delta p_i^2 \, \Delta p_j^2 \rangle$) have little effect, at least up to four loci. Correlations across loci become stronger with more loci, and so might contribute if both inbreeding and higher-order interactions are substantial: only then will moments such as $\langle \Delta p_i^2 \, \Delta p_j^2 \, \Delta p_k^2 \, \Delta p_l^2 \, \ldots \rangle$ be significant.

The contribution of dominance to the increase in additive variance for small $F$ (Eq. 51) comes through two terms, $2V_D$ and $2C_{\mathrm{AD}}$; the latter consists of two sums. The first sum in $2C_{\mathrm{AD}}$ is $4C = 4\sum_i p q_i (q_i - p_i) b_{i_m i_F} b_{i_m}$ (Cockerham and Tachida (1988) denote C by $d_i$). We can set bounds on the contribution of 4C by assuming complete dominance, with the $X_i = 1$ allele recessive. Then, $b_{i_m} = p_i b_{i_m i_F}$ (Eq. 8), and we have $4C = 4 \sum_i p_i^2 q_i (q_i - p_i) b_{i_m i_F}^2$. If recessive alleles are rare ($p_i << 1$), then this is approximately $4V_D$. Thus, this term can contribute up to twice the direct contribution of dominance ($2V_D$) if recessive alleles are rare. This does not require any overall inbreeding depression: $\sum_i p q_i b_{i_m i_F}$ could be zero if the sign of $b_{i_m i_F}$ fluctuates across loci. Thus, even for small $F$, the relative contributions of dominance and epistasis to the increase in additive variance are difficult to predict. They depend on the relative magnitudes of $V_{\mathrm{AA}}$ and $V_D$ as well as the terms in $C_{\mathrm{AD}}$ that can be comparable to $V_D$.

Experiments to date do not distinguish between dominance and epistasis as causes of increased additive variance after bottlenecks. Bryant et al. (1986) have argued that because they observed additive variance to increase most with intermediate inbreeding, epistasis is more likely to have been responsible than dominance. However, Willis and Orr (1993) point out that dominance is consistent with their observations, given the large sampling and evolutionary variances. Moreover, our analytical results show that there is no simple relationship between $F$ and the relative contributions of different variance components. More recently, Wang et al. (1998) have argued that the results of mutation accumulation experiments in *Drosophila melanogaster* imply that dominance alone can account for increased additive variance in viability after bottlenecks.

Our theoretical results show that even in the simplest case of small $F$, the expected change in variance cannot be predicted from the additive, dominance and epistatic variance components in the base population. Moreover, higher-order variances and covariances that are undetectably weak could make a large contribution to the expected additive variance with strong inbreeding. (This is because in diploids, the contribution of $k$th-order epistasis is multiplied by a factor $2^k$; see Eq. 44.) Empirical attempts to understand the relationship between $F$ and either $\mathrm{Var}(\Delta\bar{z})$ or $\langle V_A^* \rangle$ are inherently extremely difficult because the effects of drift on trait means and additive variances are highly variable (Whitlock 1995).

Drift-induced inflation of additive genetic variance has received considerable attention, because it might allow populations that survive bottlenecks to adapt more readily to new conditions or facilitate movement to new "adaptive peaks." However, there are several difficulties with these conjectures. First, estimates of genetic variance are notoriously inaccurate, and the effects of drift on genetic variance are highly variable (Avery and Hill 1977, Bulmer 1980, Lynch 1988). Thus, increases in additive variance can occur even if allelic effects are purely additive (Whitlock 1995). Indeed, if one uses as a baseline the expected variance from a purely additive model, then about half the time, the observed additive variance will exceed this expectation. For example, Cheverud et al. (1999) observed that after 55 replicate populations of mice were reduced to $N = 4$ individuals for four generations, the average additive genetic variance was essentially the same as in control populations and significantly larger (75%) than the reduced value expected with purely additive allelic effects. However, they pointed out that there is a 3% chance that such an apparent increase would be seen even if the true additive variance remained constant. Moreover, even with additivity, the underlying additive variance might by chance increase with drift (Whitlock 1995, Whitlock and Fowler 1999).

Second, if the increased variance is due to an increased frequency of rare recessive alleles, those alleles are likely to have been rare because they are deleterious. If so, one would expect selection to eliminate the excess variance, so that there would be no long-term consequences. Finally, an increased genetic variance will make little long-term difference to the population if selection favors a single optimal phenotype. Heritable variation is usually high enough for the response to selection to be rapid; and even if additive genetic variance is very low, the population will eventually reach the adaptive peak. A bottleneck will have long-term effects only if it takes the population into the domain of attraction of a new equilibrium. Thus, we should be concerned not with the genetic variance alone, but with the distribution of the trait mean and variance, plus whatever other variables determine the dynamics of the population. The choice may be between alternative adaptive peaks, or it may

be between adaptation to new conditions and extinction (Lande and Shannon 1996, Holt and Gomulkiewicz 1997). In either case, the effect of a bottleneck should be judged by whether it leads to a new stable state, rather than whether it leads to an immediate increase in additive variance. Given the many alternative ways in which populations can reach different adaptive peaks (reviewed in Coyne et al. 1997, 2000) — most obviously through changes in the environment – and the many speciation-facilitating effects that may be experienced by isolated populations (Turelli et al. 2001), it is unclear why so much attention has been lavished on drift-induced changes.

For some evolutionists, descriptions of epistasis and its possible consequences have achieved almost mystical status. Several authors seem to believe that if epistasis can be demonstrated to be pervasive and to contribute plausibly to increased additive variance after population bottlenecks, this will make theories of adaptation and speciation that have no significant empirical or theoretical support more credible (e.g., Cheverud 2000, Templeton 2000, Wade 2000). As noted in our introduction, there is plenty of empirical and theoretical evidence that epistasis is pervasive. Moreover, as we and others have shown, there are plausible circumstances under which epistasis can contribute to increases in additive variance after a population bottleneck. However, these are necessary but far-from-sufficient conditions for the shifting balance theory to be a credible explanation of adaptation or for drift-based theories, such as Mayr's (1963) "genetic revolutions," to be credible explanations for the origin of species. Indeed, these arguments are no more convincing than claiming that pigs can fly, because parts of pigs (e.g., American footballs) have been seen in the air. As we have repeatedly stressed (e.g., Coyne et al. 1997, 2000), there are no serious models of selection on polygenic traits that ignore epistasis for fitness. One of the simplest models, namely stabilizing selection on an additive polygenic trait, shows all of the central characteristics that devotees of epistasis extol: namely, the fitness effects of alleles depend both quantitatively and qualitatively on the genetic background, many equilibria are possible, and both initial conditions and the effects of drift are frequently decisive in determining the genotypes prevalent near equilibria. In general, “peak shifts” may require changes in the mean, changes in the variance, both or neither. We don’t know enough about fitness landscapes or their temporal dynamics to say. Hence, the enthusiasm for increases in $V_A$ seems misplaced. There are several fundamental areas in evolution in which epistasis clearly plays a central role, such as the genetics of postzygotic isolation (Turelli and Orr 2000) and theories of the evolution of sexual reproduction (Peters and Lively 2000). It is time to move beyond claims that theoreticians ignore epistasis and that the existence of epistasis somehow buttresses theories that are untenable for other reasons.

The methods that we have used to understand the effects of random drift on quantitative traits may be useful for problems of wider evolutionary significance. We have used a general representation of epistasis (Barton and Turelli 1991, Kirkpatrick et al. 2002) that makes no assumptions about the pattern of gene interaction. In the tradition of quantitative genetics, we show that, at least for small levels of inbreeding, observable quantities depend on just a few parameters. (For haploids, or diploids with no dominance, the outcome depends solely on the variance components, while for diploids in general, the outcome also depends on interaction terms related to the distribution of inbreeding depression across loci.) We believe that our description of epistasis will facilitate progress on other questions – for example, why the additive model gives an accurate description of most quantitative variation, how epistasis affects the maintenance of variation (cf. Hermisson et al. 2003) or how epistasis influences the response to selection (cf. Hansen and Wagner 2001).

## ■ Acknowledgments

We thank J. A. Coyne, T. F. Hansen, R. Haygood, J. Hermisson, D. Houle, J. H. Gillespie, M. Kirkpatrick, C. H. Langley, J. G. Mezey, G. P. Wagner and an anonymous reviewer for comments on earlier drafts and useful discussions. We are grateful to the Erwin Schrödinger Institute for Mathematical Physics in Vienna for support during Winter 2002. NB acknowledges support from the EPSRC/BBSRC grant MMI09726, MT acknowledges support from NSF grant DEB-0089716.

## Literature cited

Avery, P. J., and W. G. Hill. 1977. Variability in genetic parameters among small populations. Genet. Res. Camb. 29:193-213.

Barton, N. H., and M. Turelli. 1991. Natural and sexual selection on many loci. Genetics 127:229-255.

Bryant, E. H., S. A. McCommas, and L. M. Combs. 1986. The effect of an experimental bottleneck upon additive genetic variation in the housefly. Genetics 114:1191-1211.

Bulmer, M. G. 1980. The mathematical theory of quantitative genetics. Oxford Univ. Press, New York.

Cheverud, J.M. 2000. Detecting epistasis among quantitative trait loci. Pp. 58-81 *in* J. B. Wolf et al., eds. Epistasis and the evolutionary process. Oxford Univ. Press, New York.

Cheverud, J.M., and E.J. Routman. 1995. Epistasis and its contributions 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.

Cheverud, J. M., T. T. Vaughn, L. S. Pletscher, K. King-Ellison, J. Bailiff, E. Adams, C. Erickson, and A. Bonislawski. 1999. Epistasis and the evolution of additive genetic variance in populations that pass through a bottleneck. Evolution 53:1009-1018.

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.

Cockerham, C. C. 1984. Covariances of relatives for quantitative characters with drift. Pp. 195-208 in A. Chakravarti, ed. Human population genetics: the Pittsburgh Symposium. Van Nostrand Reinhold, New York.

Cockerham, C. C., and H. Tachida. 1988. Permanency of response to selection for quantitative characters in finite populations. Proc. Natl. Acad. Sci. USA 85:1563-1565.

Coyne, J. A., N. H. Barton, and M. Turelli. 1997. A critique of Wright's shifting balance theory of evolution. Evolution 51:643-671.

____. 2000. Is Wright's shifting balance process important in evolution? Evolution 54:306-317.

Crow, J. F. and M. Kimura. 1970. An Introduction to Population Genetics Theory. Harper & Row, New York.

Dobzhansky, T., 1937 Genetics and the Origin of Species. Columbia Univ. Press, New York.

Fisher, R.A. 1918. The correlation between relatives under the supposition of Mendelian inheritance, Trans. Roy. Soc. Edinburgh 52:399-433.

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

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

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

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.

Holt, R. D., and R. Gomulkiewicz. 1997. How does immigration affect local adaptation? A re-examination of a familiar paradigm. Am. Nat. 149:563-572.

Keightley, P. D. 1989. Models of quantitative variation of flux in metabolic pathways. Genetics 121:869-876.

Kempthorne, O. 1954. The correlation between relatives in a random mating population. Proc. Roy. Soc. (London) B 143:103-113.

_____. 1957. An introduction to genetic statistics. Wiley, New York.

Kirkpatrick, M., T. Johnson, and N. H. Barton. 2002. General models of multilocus evolution. Genetics 161:1727-1750.

Lande, R., and S. Shannon. 1996. The role of genetic variation in adaptation and population persistence in a changing environment. Evolution 50:434-437.

Lopez-Fanjul, C., and A. Villaverde. 1989. Inbreeding increases genetic variance for viability in D. melanogaster. Evolution 43:1800-1804.

Lopez-Fanjul, C., A. Fernandez, and M. A. Toro. 2002. The effect of epistasis on the excess of the additive and nonadditive variances after population bottlenecks. Evolution 56:865-876.

Lynch, M. 1988. Design and analysis of experiments on random drift and inbreeding depression. Genetics 120:791-807.

Lynch, M., and J. B. Walsh. 1998. Genetics and analysis of quantitative traits. Sinauer Press, Sunderland, MA.

Mayr, E. 1963. Animal species and evolution. Harvard Univ.Press. Cambridge

Muller, H. J. 1940. Bearing of the Drosophila work on systematics, Pp. 185-268 *in* J. Huxley, ed. The new systematics. Clarendon Press, Oxford.

Naciri-Graven, Y., and J. Goudet. 2003. The additive genetic variance after bottlenecks is affected by the number of loci involved in epistatic interactions. Evolution 57:706-716.

Peters, A. D., and Lively, C. 2000. Epistasis and the maintenance of sex. Pp. 99-112 *in* J. B. Wolf et al., eds. Epistasis and the evolutionary process. Oxford Univ. Press, New York.

Poulton, E. B. 1908. Essays on evolution. Clarendon Press, Oxford.

Robertson, A. 1952. The effect of inbreeding on the variation due to recessive genes. Genetics 37:189-207.

Routman, E. J., and J. M. Cheverud. 1997. Gene effects on a quantitative trait: Two-locus epistatic effects measured at microsatellite markers and at estimated QTL. Evolution 51:1654-1662.

Tachida, H., and C. C. Cockerham. 1989. A building-block model for quantitative genetics. Genetics 121:839-844.

Templeton, A. 2000. Epistasis and complex traits. Pp. 41-57 *in* J. B. Wolf et al., eds. Epistasis and the evolutionary process. Oxford Univ. Press, New York

Turelli, M., and H. A. Orr. 2000. Dominance, epistasis and the genetics of postzygotic isolation. Genetics 154:1663-1679.

Turelli, M., N. H. Barton and J. A. Coyne. 2001. Theory and speciation. Trends Ecol. Evol. 16:330-343.

Wade, M. J. 2000. Epistasis as a genetic constraint within populations and an accelerant of adaptive divergence among them. Pp. 213-231 *in* J. B. Wolf et al., eds. Epistasis and the evolutionary process. Oxford Univ. Press, New York.

Wade, M. J., and C. J. Goodnight. 1998. The theories of Fisher and Wright in the context of metapopulations: when nature does many small experiments. Evolution 52:1537-1553.

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

Walsh, J.B., and Lynch, M. 1998. Genetics and analysis of quantitative traits II Sinauer Press, Sunderland, Massachusetts. http://nitro.biosci.arizona.edu/zbook/volume_2/vol2.html

Wang, J. L., A. Caballero, P. D. Keightley, and W. G. Hill. 1998. Bottleneck effect on genetic variance: A theoretical investigation of the role of dominance. Genetics 150:435-447.

Whitlock, M. C. 1995. Variance-induced peak shifts. Evolution 49:252-259.

Whitlock, M. C., and K. Fowler. 1999. The changes in genetic and environmental variance with inbreeding in *Drosophila melanogaster*. Genetics 152:345-353.

Whitlock, M. C., P. C. Phillips, and M. J. Wade. 1993. Gene interaction affects the additive genetic variance in subdivided populations with migration and extinction. Evolution 47:1758-1769.

Willis, J. H., and H. A. Orr. 1993. Increased heritable variation following population bottlenecks: the role of dominance. Evolution 47:949-956.

Wright, S., 1935 Evolution of populations in approximate equilibrium. J. Genet. 30: 257-266.

## Appendix 1: Conditional expectations

As demonstrated in the text, the effect associated with the genotype carrying 0 alleles at positions $i \in \mathbb{S}_0$ and 1 alleles at positions $i \in \mathbb{S}_1$, denoted $\alpha_{\mathbb{S}_0\,\mathbb{S}_1}$, is $b_{\mathbb{S}}(-p)_{\mathbb{S}_o}\, q_{\mathbb{S}_1}$ with $\mathbb{S} = \mathbb{S}_0\,\mathbb{S}_1$. Because this genotype has frequency $q_{\mathbb{S}_0}\, p_{\mathbb{S}_1}$ and $E[\alpha_{\mathbb{S}}] = 0$, we see that

$$\begin{aligned} \mathrm{Var}(\alpha_{\mathbb{S}}) &= E[\alpha_{\mathbb{S}}^2] = \sum_{\mathbb{S}_0\,\mathbb{S}_1=\mathbb{S}} [b_{\mathbb{S}}(-p)_{\mathbb{S}_0}\, q_{\mathbb{S}_1}]^2\, q_{\mathbb{S}_0}\, p_{\mathbb{S}_1} \\ &= b_{\mathbb{S}}^2 (pq)_{\mathbb{S}} \sum_{\mathbb{S}_0\,\mathbb{S}_1=\mathbb{S}} p_{\mathbb{S}_0}\, q_{\mathbb{S}_1} = b_{\mathbb{S}}^2 (pq)_{\mathbb{S}} \prod_{i\in\mathbb{S}} (p_i + q_i) \\ &= b_{\mathbb{S}}^2 (pq)_{\mathbb{S}} \end{aligned} \qquad (52)$$

for every set $\mathbb{S}$. Given this simple form and our general expression for $V_G$, it follows that finding the components of variance reduces to identifying the sets $\mathbb{S}$ that contribute to the component in question.

For example, with haploids, $V_A$ is simply the sum of the variances associated with each individual locus, i.e.,

$$V_A = \sum_{i\in\mathbb{Z}} b_i^2\, p_i\, q_i . \qquad (53)$$

Similarly, $V_{AA}$ is the sum of $\mathrm{Var}(\alpha_{\{i,j\}})$ for all pairs of distinct elements {i,j}. The only complication introduced by diploidy is recognizing that additive effects can be associated with either paternally or maternally inherited alleles. This introduces factors of 2, as discussed in the text.

## Appendix 2: Multilocus moments

The effect of genetic drift on genotype frequencies in a population can be described by the $D_U$, defined relative to the initial allele frequencies $p_i$. The $D_i$ give the change in allele frequency, while higher-order *Ds* describe the linkage disequilibria. Assuming $k$ diallelic loci, the sets $U$ run over all $2^k - 1$ distinct subsets of loci, Z = {1, 2, ..., $k$}; for instance, they might be ordered {{1}, {2}, ..., {k}, {1,2}, {1,3}, ..., {k-1,k}, {1,2,3}, ..., {1,2,3,...k}}. To produce a simple recursion for the moments of the multilocus associations under recombination and drift, define

$$M[\underline{a}] \equiv \langle \underline{D}^{\underline{a}} \rangle, \text{ where } \underline{D}^{\underline{a}} \equiv \prod_{U \subseteq Z} D_U^{a_U}. \tag{54}$$

Here, $\underline{a}$ is a vector of $2^k - 1$ integers that gives the power to which each $D_U$ is raised in the moment $M$, according to a natural ordering of the subsets U, such as the one specified above. For example, the variance in allele frequency at locus $i$ is $\langle D_i^2 \rangle = M[\underline{a}]$ with $a_U = 2$ for $U = \{i\}$ and $a_U = 0$ for $U \neq \{i\}$. Let $|a| \equiv \sum_{U \subseteq Z} a_U$. The rate at which recombination brings together a set of genes $S$ from one genome and $T$ from the other is $r_{S|T}$. We scale recombination rates relative to the rate of random drift, using $R_{S|T} = 2Nr_{S|T}$.

A differential equation for the moments can be derived from the multilocus diffusion approximation. The forward diffusion for the multivariate distribution of $\underline{D}$, $\psi[\underline{D}]$, is (Ewens 1979)

$$\partial_t \psi = \sum_{U \subseteq Z} \frac{\partial}{\partial D_U} \left( -M_U \psi + \frac{1}{2} \sum_{V \subseteq Z} \frac{\partial}{\partial D_V} (C_{UV} \psi) \right), \tag{55}$$

where the expected change in $D_U$ due to recombination is $M_U = \sum_{ST=U} R_{S|T}(D_S D_T - D_U)$, and the covariance between fluctuations in $D_U$ and $D_V$ is $C_{UV} = D_{UV} - D_U D_V$ (Turelli and Barton, 1990, Eq. A1.22). Substituting into Eq. 55, multiplying by $\underline{D}^{\underline{a}}$, and integrating over $\underline{D}$, we obtain

$$\partial_t M[\underline{a}] = \int \sum_{U \subseteq Z} \underline{D}^{\underline{a}} \frac{\partial}{\partial D_U} \left( -\sum_{ST=U} R_{S|T} (D_S D_T - D_U) \psi + \frac{1}{2} \sum_{V \subseteq Z} \frac{\partial}{\partial D_V} ((D_{UV} - D_U D_V) \psi) \right) d\underline{D}. \tag{56}$$

Integrating by parts, using $\frac{\partial D^{\underline{a}}}{\partial D_U} = a_U \frac{D^{\underline{a}}}{D_U}$, we obtain

$$\partial_t M[\underline{a}] = \sum_{U \subseteq Z} \int \frac{a_U}{D_U} \underline{D}^{\underline{a}} \left( \sum_{ST=U} R_{S|T} (D_S D_T - D_U) \psi - \frac{1}{2} \sum_{V \subseteq Z} \frac{\partial}{\partial D_V} ((D_{UV} - D_U D_V) \psi) \right) d\underline{D} \tag{57}$$

$$= \sum_{U\subseteq Z} a_U \sum_{ST=U} R_{S|T} \left( \left\langle \underline{D}^{\underline{a}} \frac{D_S D_T}{D_U} \right\rangle - M[\underline{a}] \right) -$$

$$\frac{1}{2} \sum_{U\subseteq Z} \int \frac{a_U}{D_U} \underline{D}^{\underline{a}} \sum_{V\subseteq Z} \frac{\partial}{\partial D_V} \left( (D_{UV} - D_U D_V) \psi \right) d\underline{D}.$$

Integrating by parts again to simplify the second term, we obtain

$$\partial_t M[\underline{a}] = \sum_{U\subseteq Z} a_U \sum_{ST=U} R_{S|T} \left( \left\langle \underline{D}^{\underline{a}} \frac{D_S D_T}{D_U} \right\rangle - M[\underline{a}] \right) +$$

$$\frac{1}{2} \sum_{U,V\subseteq Z} a_U (a_V - \delta_{U,V}) \left( \left\langle \underline{D}^{\underline{a}} \frac{D_{UV}}{D_U D_V} \right\rangle - M[\underline{a}] \right). \qquad (58)$$

with all $M$ zero initially. The expectations in Eq. 58 are moments with different indices. The first expectation, for example, has $a_S$, $a_T$ each incremented by 1, and $a_U$ decremented by 1, and could be written $M[\underline{a} + \underline{\delta}_S + \underline{\delta}_T - \underline{\delta}_U]$ where $\underline{\delta}_U$ is a vector with $\delta_U = 1$ and all other entries zero. The second expectation must be simplified using the assumption of two alleles per locus.

We can apply Eq. 5 of Barton and Turelli (1991), to see that if A, B and C are disjunct sets without repeated indices,

$$D_{ABCC} = \langle \zeta_{AB} \prod_{i\in C} (pq_i - \Delta_i \zeta_i) \rangle = \sum_{XY=C} pq_X (-\Delta)_Y D_{ABY}, \qquad (59)$$

with $\Delta_i = p_i - q_i$. For any sets U and V, we can apply this reduction with C = U⋂V, A = U\C, and B = V\C (so that $U = AC$ and $V = BC$). Hence,

$$\partial_t M = \sum_U a_U \left( \sum_{ST=U} R_{S|T} \left\langle \underline{D}^{\underline{a}} \frac{D_S D_T}{D_U} \right\rangle - M \right) +$$

$$\frac{1}{2} \sum_{U,V} a_U (a_V - \delta_{U,V}) \left( \sum_{XY=U\cap V} pq_X (-\Delta)_Y \left\langle \underline{D}^{\underline{a}} \frac{D_{ABY}}{D_U D_V} \right\rangle - M \right). \qquad (60)$$

We can show from this recursion that moments are non-zero only when every locus appears more than once. To see this, consider the two terms in Eq. 58 due to recombination and drift. The first term relates moments involving sets of multiple loci to moments with elements that are partitions of these sets (for example, $\langle D_{\{i,j,k\}} D_{\{i\}} \rangle$ is related to $\langle D_{\{i,j\}} D_{\{k\}} D_{\{i\}} \rangle$). The second term involves contributions from associations between $D$s

involving unions of two sets (for example, $\langle D_{\{i,j,k\}}\, D_{\{i\}}\rangle$ is related to $\langle D_{\{i,i,j,k\}}\rangle$). In both cases, the set of loci involved remains the same ($\{i, i, j, k\}$ in these examples). Non-zero contributions can arise only from disequilibria in which all indices are repeated (for example, $D_{\{i,i,j,j\}}$), and these reduce to expressions involving products of $pq$s. This reduction process can eliminate multiple entries of loci, but cannot eliminate loci that appear only once. Thus, any moment in which any locus appears just once must depend only on other moments in which that locus appears just once, and since all such moments are initially zero, they will remain zero.

To illustrate the method, we set out the recursions required to solve for $\left\langle \Delta p_i^2\, \Delta p_j^2 \right\rangle$. These recursions depend on all other moments that involve the same set of loci, {i,i,j,j}: $\langle D_{ij}^2\rangle$, $\left\langle D_{ij}\, \Delta p_i\, \Delta p_j \right\rangle$, $\left\langle D_{ii}\, \Delta p_j^2 \right\rangle$, $\langle D_{jj}\, \Delta p_i^2\rangle$, $\langle D_{iijj}\rangle$. The last three reduce down to depend on $\langle \Delta p_i^2\rangle$, $\left\langle \Delta p_j^2 \right\rangle$, as well as moments such as $\langle D_{iij}\rangle$ which will be zero. We thus have recursions for five non-zero moments:

$$
\begin{aligned}
&\partial_T \langle \Delta p_i^2 \rangle = pq_i - \langle \Delta p_i^2 \rangle \\
&\partial_T \langle \Delta p_j^2 \rangle = pq_j - \langle \Delta p_j^2 \rangle \\
&\partial_T \langle \Delta p_i^2\, \Delta p_j^2 \rangle = 4\,(\langle D_{ij}\, \Delta p_i\, \Delta p_j \rangle - \langle \Delta p_i^2\, \Delta p_j^2 \rangle) - 2\,\langle \Delta p_i^2\, \Delta p_j^2 \rangle \\
&\qquad + \langle \Delta p_j^2 \rangle\, pq_i + \langle \Delta p_i^2 \rangle\, pq_j \\
&\partial_T \langle D_{ij}\, \Delta p_i\, \Delta p_j \rangle = \langle D_{ij}^2 \rangle - 3\,\langle D_{ij}\, \Delta p_i\, \Delta p_j \rangle + pq_i\,\langle \Delta p_j^2 \rangle \\
&\qquad + pq_j\,\langle \Delta p_i^2 \rangle + R\,(\langle \Delta p_i^2\, \Delta p_j^2 \rangle - \langle D_{ij}\, \Delta p_i\, \Delta p_j \rangle) \\
&\partial_T \langle D_{ij}^2 \rangle = pq_i\, pq_j - \langle D_{ij}^2 \rangle + 2\,R\,(\langle D_{ij}\, \Delta p_i\, \Delta p_j \rangle - \langle D_{ij}^2 \rangle),
\end{aligned}
\qquad (61)
$$

where R is the scaled recombination rate between loci $i$, $j$.

To understand how Eqs. 61 follow from Eq. 60, consider the simplest, for $\partial_T \langle \Delta p_i^2 \rangle$. This corresponds to $a_{\{i\}} = 2$, and $a_U = 0\ \forall\ U \neq \{i\}$. Since $\langle \Delta p_i^2 \rangle$ only involves a single locus, the first term, representing recombination, does not contribute. (Formally, there is only one partition of $\{i\}$, with rate $R_{\emptyset|\{i\}} = 1$; since $\left\langle \underline{D}^a\, \frac{D_\emptyset\, D_{\{i\}}}{D_{\{i\}}} \right\rangle = \langle \underline{D}^a \rangle = M$, this term contributes nothing.) The second term represents the effect of drift. Because only $U = V = \{i\}$ contribute, and $a_{\{i\}} = 2$, the factor $\frac{1}{2} \sum_{U,V} a_U\,(a_V - \delta_{U,V}) = \frac{1}{2}\ 2 \times (2 - 1) = 1$. The sum is over all partitions $XY$ of $U \bigcap V$={i}. Recall that C = U⋂V={i}, so that A = U\C=$\emptyset$, and B = V\C=$\emptyset$. Therefore, for X={i},Y=$\emptyset$, the sum is $pq_{\{i\}}\,(-\Delta)_\emptyset\,\langle \underline{D}^a\, \frac{D_\emptyset}{D_U\, D_V} \rangle = pq_i$. For X=$\emptyset$, Y={i}, the sum is $pq_\emptyset\,(-\Delta)_{\{i\}}\,\langle \underline{D}^a\, \frac{D_{\{i\}}}{D_U\, D_V} \rangle = 0$. Putting all this together, we have $\partial_T \langle \Delta p_i^2 \rangle = pq_i - \langle \Delta p_i^2 \rangle$, as in the first of Eqs. 61.

It is simplest to solve for the Laplace Transform with respect to time, $\tilde{M} = \int_0^\infty M e^{-zT}\,\mathrm{dT}$, in which case $\partial_t \mathrm{M}$ is replaced by $-z\tilde{M}$ in Eq. 60, and constant terms are multiplied by $\frac{1}{z}$. For a pair of loci, an explicit solution can be found:

$$\int_0^T \langle \Delta p_i^2\, \Delta p_j^2 \rangle\, e^{-zT}\,\mathrm{dT} = \frac{2\,(B + 2\,z\,(1+z))}{z\,(1+z)\,(2+z)\,B}\, pq_i\, pq_j$$

$$\int_0^T \langle \Delta p_i\, \Delta p_j\, D_{ij} \rangle\, e^{-zT}\,\mathrm{dT} = \frac{(3\,B - R_{i,j}\,(13+3\,z)\,(2+z) - 2\,R_{i,j}^2\,(2+z))}{z\,(1+z)\,(2+z)\,B}\, pq_i\, pq_j \qquad (62)$$

$$\int_0^T \langle D_{ij}^2 \rangle\, e^{-zT}\,\mathrm{dT} = \frac{(B - 2\,z\,(6+z)\,R_{i,j} - 2\,z\,R_{i,j}^2)}{z\,(1+z)\,B}\, pq_i\, pq_j$$

where $B = (1+z)\,(3+z)\,(6+z) + R_{i,j}\,(2+z)\,(13+3\,z) + 2\,R_{i,j}^2\,(2+z)$.

As $R \to \infty$, $\int_0^T \langle \Delta p_i^2\, \Delta p_j^2 \rangle\, e^{-zT}\,\mathrm{dT}$ tends to $\frac{2}{z\,(1+z)\,(2+z)}$. As $R \to 0$, it tends to $\frac{2\,(9+z)}{z\,(1+z)\,(3+z)\,(6+z)}$. These limiting forms transform back to

$$\frac{\langle \Delta p_i^2\, \Delta p_j^2 \rangle}{\langle \Delta p_i^2 \rangle\, \langle \Delta p_j^2 \rangle} = 1 \text{ as } R \to \infty$$

$$\frac{\langle \Delta p_i^2\, \Delta p_j^2 \rangle}{\langle \Delta p_i^2 \rangle\, \langle \Delta p_j^2 \rangle} = 1 + \frac{F\,(1-F)}{15}\,(6 + 3\,F + F^2) \text{ as } R \to 0, \qquad (63)$$

where $F = 1 - e^{-T}$. Thus, when recombination is fast relative to drift ($R \to \infty$), the squared fluctuations are independent across loci ($\langle \Delta p_i^2\, \Delta p_j^2 \rangle = \langle \Delta p_i^2 \rangle\, \langle \Delta p_j^2 \rangle$). When linkage is tight, we are effectively following the random drift of a single multiallelic locus, but with the constraint that the initial genotype frequencies are those of a population at linkage equilibrium. The maximum is only 1.13 at $T = 0.829$ ($F = 0.563$) (Fig. 1).

Explicit formulae for more than two loci are cumbersome. However, solutions can be written down for complete linkage:

$$\frac{\langle \Delta p_i^2\, \Delta p_j^2\, \Delta p_k^2 \rangle}{\langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle \langle \Delta p_k^2 \rangle} =$$

$$1 + \frac{F\,(1-F)}{315}\,(630 + 756\,F - 3738\,F^2 + 5892\,F^3 - 5763\,F^4 + 3977\,F^5 - 2002\,F^6 + 728\,F^7 - 182\,F^8 + 28\,F^9 - 2\,F^{10})$$

$$\frac{\langle \Delta p_i^2\, \Delta p_j^2\, \Delta p_k^2\, \Delta p_l^2 \rangle}{\langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle \langle \Delta p_k^2 \rangle \langle \Delta p_l^2 \rangle} = 1 +$$

$$\frac{F\,(1-F)}{45045}\,(180180 + 582582\,F - 369798\,F^2 - 11804793\,F^3 + 55233607\,F^4 - 144969539\,F^5 + 274747213\,F^6 - 410742592\,F^7 + 505345868\,F^8 - 523438072\,F^9 + 462108348\,F^{10} - 349755705\,F^{11} + 227246175\,F^{12} - 126455355\,F^{13} + 59932665\,F^{14} - 23976342\,F^{15} + 7992270\,F^{16} - 2179710\,F^{17} + 473850\,F^{18} - 78975\,F^{19} + 9477\,F^{20} - 729\,F^{21} + 27\,F^{22})\,.$$

Associations among squared fluctuations increase substantially as more loci are involved (Fig. 2).

*Mathematica* code for automatic generation and solution of recursions such as these is available from http://helios.bto.ed.ac.uk/evolgen/

## Appendix 3: Random genotypic values

- **Haploids**

We have very little idea as to plausible values for the coefficients $b_{\mathbb{U}}$. At one extreme, we could assume complete additivity, and set all nonlinear terms to zero. At the other extreme, we can assign random trait values independently to each genotype. When genotypic values are chosen independently, we expect all levels of epistasis. To produce a normal distribution of phenotypes, we assume a normal distribution of genotypic values. In a subsequent paper, we will analyze the resulting distribution of the coefficients $b_{\mathbb{U}}$ and present analytical results that illuminate the simulations presented by Naciri-Graven and Goudet (2003). Here we use this model simply to illustrate some general properties of components of genetic variance and the consequences of bottlenecks.

- **Diploids**

A model of gene interaction in diploids must satisfy the condition that *cis* and *trans* combinations give the same trait values. One way to ensure this is to assume that the $i$th locus has an effect $Y_i$ which takes values $-p_i + p_i\ q_i(2\,d_i - 1)$, $-\frac{1}{2}\,((p_i - q_i) + (2\,d_i - 1)\,(1 - 2\,p_i\,q_i))$, $q_i + p_i\ q_i(2\,d_i - 1)$ for the three genotypes $\{X_{i_m}, X_{i_f}\} = \{0, 0\},\ \{0, 1\}, \{1, 1\}$. This choice of scaling gives pure additivity with $d_i = \frac{1}{2}$. With $d_i = 0$, the 0 allele is recessive; and with $d_i = 1$, the 1 allele is recessive. The relationship is scaled such that $E[Y_i] = 0$ so that the difference between homozygotes is 1 for all $d_i$. Note that this model is restrictive, in that the additive and dominance effects of each locus must participate in interactions with other loci in the same way (i.e., via a single dominance coefficient $d_i$).

We assign values to diploid genotypes by drawing the homozygous values at random,from a Gaussian distribution with mean zero and variance $\sigma_z^2$. To find an expression for the $c_U$ in terms of these randomly drawn homozygous values, we construct a hypothetical population which contains only homozygotes. Genotype frequencies are at linkage equilibrium, and allele frequency at locus $i$ is set to $P_i = p_i(1 - (2\,d_i - 1)\,q_i)$. This choice ensures that $\tilde{E}[Y_i] = 0$, where $\tilde{E}[]$ denotes an expectation over the hypothetical population of homozygotes. The coefficient $c_U$ is the regression of the trait on the product $Y_U$.

## Appendix 4: Changes in trait mean and genetic variance in diploids

- **Variance of the trait mean**

After a bottleneck, the average of the squared change of the trait mean is $\langle(\Delta\,\bar{z}^2)\rangle = \sum_{\mathbb{U}\neq\varnothing}\sum_{\mathbb{V}\neq\varnothing} \mathtt{b}_{\mathbb{U}}\ \mathtt{b}_{\mathbb{V}}\ \langle\,\triangle\mathtt{p}_{\mathbb{U}}\ \triangle\mathtt{p}_{\mathbb{V}}\,\rangle$ (Eq. 21). However, the sum is now over all sets of diploid positions $\mathbb{U}$, $\mathbb{V}$; and these may contain one or two contributions from each locus (e.g., $\mathbb{U} = \{i_m, i_f, j_m\}$. We seek sets $\mathbb{U}$, $\mathbb{V}$ for which $\langle\,\triangle\mathtt{p}_{\mathbb{U}}\ \triangle\mathtt{p}_{\mathbb{V}}\,\rangle$ is non-zero, making the approximation of statistical independence across loci, and assuming $\langle\Delta\mathrm{p}_i\rangle = 0$. To simplify the accounting, let $b_{\mathbb{U}} = b_{A|B}$, where A is the set of loci for which only one of $i_m$ or $i_f$ appears and B is the set of loci for which both $i_m$ and $i_f$ appear. Enumerating terms of successively higher order in Eq. 21, and invoking the assumption that there is no difference between *cis* and *trans*:

$$
\begin{aligned}
\langle (\Delta \bar{z})^2 \rangle = \; & 4 \sum_i b^2_{\{i\}|\emptyset} \langle \Delta p_i^2 \rangle \\
& + 4 \sum_i b_{\{i\}|\emptyset}\, b_{\emptyset|\{i\}} \langle \Delta p_i^3 \rangle + \sum_i b^2_{\emptyset|\{i\}} \langle \Delta p_i^4 \rangle \\
& + 8 \sum_{i \neq j} \left( b_{\{i\}|\emptyset}\, b_{\{i\}|\{j\}} + b^2_{\{i,j\}|\emptyset} \right) \langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle \\
& + 4 \sum_{i \neq j} \left( 4\, b_{\{i,j\}|\emptyset}\, b_{\{j\}|\{i\}} + b_{\emptyset|\{i\}}\, b_{\{i\}|\{j\}} \right. \\
& \qquad \left. + b_{\{i\}|\emptyset}\, b_{\emptyset|\{i,j\}} \right) \langle \Delta p_i^3 \rangle \langle \Delta p_j^2 \rangle \\
& + 4 \sum_{i \neq j} \left( b_{\{i,j\}|\emptyset}\, b_{\emptyset|\{i,j\}} + b_{\{i\}|\{j\}}\, b_{\{j\}|\{i\}} \right) \\
& \qquad \langle \Delta p_i^3 \rangle \langle \Delta p_j^3 \rangle \\
& + 2 \sum_{i \neq j} \left( 2\, b^2_{\{j\}|\{i\}} + b_{\emptyset|\{i\}}\, b_{\emptyset|\{i,j\}} \right) \langle \Delta p_i^4 \rangle \langle \Delta p_j^2 \rangle \\
& + 4 \sum_{i \neq j} b_{\{j\}|\{i\}}\, b_{\emptyset|\{i,j\}} \langle \Delta p_i^4 \rangle \langle \Delta p_j^3 \rangle \\
& + \sum_{i \neq j} b^2_{\emptyset|\{i,j\}} \langle \Delta p_i^4 \rangle \langle \Delta p_j^4 \rangle \\
& \ldots
\end{aligned}
\tag{65}
$$

All terms involving one or two loci are shown. The factors of $2^k$ are tricky to work out. One must count all equivalent coefficients (e.g. $b_{i_m j_m}$, $b_{i_m j_f}$, $b_{i_f j_m}$, $b_{i_f j_f}$ etc.) and also count asymmetric sums such as $\sum_i b_{i_m} b_{i_m, i_f}$ twice, because we could have $\mathbb{U} = \{i_m\}$, $\mathbb{V} = \{i_m, i_f\}$ or the converse. Also, when the terms being summed are symmetrical in $i$ and $j$, the double sum over $i \neq j$ effectively introduces a factor of 2. (Here, for compactness, we allow both $b_{\{i,j\}|\emptyset}$ and $b_{\{j,i\}|\emptyset}$ to appear in the double sum and assign them the same value. This can cause some confusion in the accounting, because now, for instance, $V_{\mathrm{AA}} = 2 \sum_{i \neq j} b^2_{\{i,j\}|\emptyset}\, \mathrm{pq}_{\mathrm{ij}}$, instead of the expression given in (15).) As a check on our bookkeeping, all 462 distinct components for five loci were generated symbolically, in terms of arbitrary $\Delta p_i$; these summed correctly to the total squared change in mean for a particular choice of $\Delta p_i$.

Substituting for the moments of allele frequency from Eq. 37,

$$
\begin{aligned}
&\langle (\Delta \bar{z})^2 \rangle = 4F \sum_i b^2_{\{i\}|\emptyset}\, pq_i \\
&+2F^2 (3-F) \sum_i b_{\{i\}|\emptyset}\, b_{\emptyset|\{i\}}\, pq_i (q_i - p_i) \\
&+\tfrac{F^2}{5} \sum_i b^2_{\emptyset|\{i\}}\, pq_i (A + B\, pq_i) \\
&+8F^2 \sum_{i\neq j} (b_{\{i\}|\emptyset}\, b_{\{i\}|\{j\}} + b^2_{\{i,j\}|\emptyset})\, pq_{ij} \\
&+2F^3 (3-F) \\
&\quad \sum_{i\neq j} (4\, b_{\{i,j\}|\emptyset}\, b_{\{j\}|\{i\}} + b_{\emptyset|\{i\}}\, b_{\{i\}|\{j\}} + b_{\{i\}|\emptyset}\, b_{\emptyset|\{i,j\}}) \\
&\qquad (q_i - p_i)\, pq_{ij} \qquad (66) \\
&+F^4 (3-F)^2 \sum_{i\neq j} (b_{\{i,j\}|\emptyset}\, b_{\emptyset|\{i,j\}} + b_{\{i\}|\{j\}}\, b_{\{j\}|\{i\}}) \\
&\qquad (q_i - p_i)(q_j - p_j)\, pq_{ij} \\
&\tfrac{+2F^3}{5} \sum_{i\neq j} (2\, b^2_{\{i\}|\{j\}} + b_{\emptyset|\{i\}}\, b_{\emptyset|\{i,j\}})\, pq_{ij} (A + B pq_i) \\
&+\tfrac{2F^4}{5} (3-F) \sum_{i\neq j} b_{\{j\}|\{i\}}\, b_{\emptyset|\{i,j\}} (q_j - p_j)\, pq_{ij} (A + B pq_i) \\
&+\tfrac{F^4}{25} \sum_{i\neq j} b^2_{\emptyset|\{i,j\}}\, pq_{ij} (A + B pq_i)(A + B pq_j) \\
&\ldots
\end{aligned}
$$

where $A = F(15(1-F) + 6F^2 - F^3)$, $B = 5(3 - 16F + 15F^2 - 6F^3 + F^4)$. Some, but not all, terms in this expression can be written in terms of the variance components (Eq. 38).

Finally, we set $\mathrm{Var}(\Delta \bar{z}) = \langle (\bar{z})^2 \rangle - \langle \bar{z} \rangle^2$, where $\langle \bar{z} \rangle$ is given by (34). Keeping only the terms involving one or two loci, we have

$$
\begin{aligned}
\langle \Delta \bar{z} \rangle &= F \sum_i b_{\emptyset|\{i\}}\, \mathrm{pq}_i + F^2 \sum_{i\neq j} b_{\emptyset|\{i,j\}}\, \mathrm{pq}_{ij} + \ldots, \text{ so that} \\
\langle \Delta \bar{z} \rangle^2 &= F^2 \sum_i b^2_{\emptyset|\{i\}}\, \mathrm{pq}_i^2 + F^2 \sum_{i\neq j} b_{\emptyset|\{i\}}\, b_{\emptyset|\{j\}}\, \mathrm{pq}_{ij} + \qquad (67) \\
&\qquad 2F^3 \sum_{i\neq j} b_{\emptyset|\{i\}}\, b_{\emptyset|\{i,j\}}\, \mathrm{pq}_i\, \mathrm{pq}_{ij} + F^4 \sum_{i\neq j} b^2_{\emptyset|\{i\}}\, \mathrm{pq}_i^2 + \ldots
\end{aligned}
$$

Note that the first term in $\langle \Delta \bar{z} \rangle^2$ is $F^2\, V_D$ and the fourth term is $F^4\, V_{\mathrm{DD}}$. Subtracting (81) from (80) and identifying variance components, we obtain (38).

- **Change in additive genetic variance**

Our expressions for the additive variance (15) and for the effects of allele frequencies changes on the $b_{\mathbb{U}}$ (3) imply that the expected additive genetic variance after a bottleneck is

$$
\langle V_A^* \rangle = \sum_{\mathbb{i}} \sum_{\mathbb{U},\mathbb{V}\subseteq\mathbb{Z}\setminus\mathbb{i}} b_{\mathbb{i}\mathbb{U}}\, b_{\mathbb{i}\mathbb{V}}\, \langle pq_{\mathbb{i}}^*\, \Delta p_{\mathbb{U}}\, \Delta p_{\mathbb{V}} \rangle . \qquad (68)
$$

The sets $\mathbb{U},\mathbb{V}$ can each contain at most one copy of the locus $i$. (For example, if $\mathbb{i} = i_m$, each of the sets $\mathbb{U},\mathbb{V}$ can contain $i_f$). This can be rearranged by choosing arbitrarily the case $\mathbb{i} = i_m$,

and noting that the complementary case $\mathbb{i} = i_f$ will give the same contribution. We also separate out the cases where the sets $\mathbb{U}$, $\mathbb{V}$ do not contain the locus $i$, where one or the other does, and finally where both do and substitute $pq_i^* = (pq_i + (q_i - p_i)\,\Delta p_i - \Delta p_i^2)$ to obtain

$$\begin{aligned}\langle V_A^* \rangle = 2 \sum_i \sum_{\mathbb{U},\mathbb{V} \subseteq \mathbb{Z} \setminus \{i_m, i_f\}} & \left( b_{\{i_m\}\mathbb{U}}\, b_{\{i_m\}\mathbb{V}} \left\langle (pq_i - \Delta p_i^2) \right\rangle + \right. \\ & \left( b_{\{i_m\}\mathbb{U}}\, b_{\{i_m, i_f\}\mathbb{V}} + b_{\{i_m, i_f\}\mathbb{U}}\, b_{\{i_m\}\mathbb{V}} \right) \\ & \left\langle (q_i - p_i)\,\Delta p_i^2 - \Delta p_i^3 \right\rangle + \\ & \left. b_{\{i_m, i_f\}\mathbb{U}}\, b_{\{i_m, i_f\}\mathbb{V}} \left\langle pq_i\,\Delta p_i^2 + (q_i - p_i)\,\Delta p_i^3 - \Delta p_i^4 \right\rangle \right) \\ & \left\langle \Delta p_{\mathbb{U}}\,\Delta p_{\mathbb{V}} \right\rangle \end{aligned}$$

$$\begin{aligned} = 2\,(1 - F) \sum_i pq_i & \sum_{\mathbb{U},\mathbb{V} \subseteq \mathbb{Z} \setminus \{i_m\, i_f\}} \left\langle \Delta p_{\mathbb{U}}\,\Delta p_{\mathbb{V}} \right\rangle \\ & \left( b_{i_m \mathbb{U}}\, b_{i_m \mathbb{V}} + \right. \\ & \left( b_{i_m i_f \mathbb{U}}\, b_{i_m \mathbb{V}} + b_{i_m \mathbb{U}}\, b_{i_m i_f \mathbb{V}} \right) \frac{F}{2}\,(2 - F)\,(q_i - p_i) + \\ & \left. b_{i_m i_f \mathbb{U}}\, b_{i_m i_f \mathbb{V}}\, \frac{F}{10}\,(C + D\,pq_i) \right), \end{aligned} \tag{69}$$

where $C = F\,(15 - 20\,F + 10\,F^2 - 2\,F^3)$ and $D = 10\,(1 - 8\,F + 10\,F^2 - 5\,F^3 + F^4)$. This expression is still complicated, because there can be contributions whenever the sets $\mathbb{U}$, $\mathbb{V}$ contain loci that appear two, three or four times. Just as for the variance in trait mean, there will be terms that do not depend solely on the variance components.

The first few terms, corresponding to the lowest powers of F, contributed by $\{\mathbb{U}, \mathbb{V}\} = \{\emptyset, \emptyset\}$, $\{\{j_m\}, \{j_m\}\}$, $\{\{j_m, j_f\}, \emptyset\}$ are:

$$\begin{aligned} \langle V_A^* \rangle = & \\ & 2\,(1 - F) \sum_i pq_i \left( b_{i_m}^2 + b_{i_m i_f}\, b_{i_m}\, F\,(2 - F)\,(q_i - p_i) + \right. \\ & \left. b_{i_m i_f}^2\, \frac{F}{10}\,(C + D\,pq_i) \right) \\ & + 8\,(1 - F)\,F \sum_{i \neq j} pq_{ij} \left( b_{i_m j_m}^2 + \right. \\ & b_{i_m i_f j_m}\, b_{i_m j_m}\, F\,(2 - F)\,(q_i - p_i) + \\ & \left. b_{i_m i_f j_m}^2\, \frac{F}{10}\,(C + D\,pq_i) \right) \end{aligned} \tag{70}$$

$$+4\,(1-F)\,F\sum_i pq_{ij}\,\Big(b_{i_m j_m j_f}\,b_{i_m} + (b_{i_m i_f j_m j_f}\,b_{i_m} + b_{i_m j_m j_f}\,b_{i_m i_f})\,\frac{F}{2}\,(2-F)\,(q_i - p_i) + b_{i_m i_f j_m j_f}\,b_{i_m i_f}\,\frac{F}{10}\,(C + D\,pq_i)\Big) + \ldots$$

Identifying those terms that can be expressed as variance components leads to Eq. 48.

## Appendix 5: Relation with two-locus analyses

Walsh and Lynch (1998, Ch. 3, Table 2) summarize Cockerham and Tachida's (1988) results for two loci. The expected additive genetic variance is:

$$\begin{aligned}\langle V_A^* \rangle \;=\; & (1-f)\,\sigma_A^2 \;+\; 2\,(f - \gamma - 2\,(\Delta - \delta))\,\sigma_D^2 \;+\\ & 2\,(f-\gamma)\,\sigma_{ADI}^2 + 2\,(\gamma - \delta)\,\sigma_{DI}^2 \;+\\ & 2\,(\gamma - \Delta)\,i^* + 2\,(\bar{\gamma} - \bar{\Delta})\,(i^2 - i^*)\\ & \qquad + (4\,f - \bar{f} - 2\,\bar{\gamma} - \bar{\Delta})\,\sigma_{AA}^2,\end{aligned} \tag{71}$$

where $f$ is equivalent to our $F$, and $\gamma$, $\Delta$ and $\delta$ are identity coefficients among three and four genes at a single locus. Coefficients with an overbar involve two loci; assuming linkage equilibrium throughout, these all reduce to $F^2$. Walsh and Lynch (1998, Ch. 3, Eq. 2.3) gives the single-locus coefficients as functions of time. Rewriting these in terms of F, and neglecting terms of order $1/N_e^2$ or smaller, we have:

$$\gamma = \frac{F^2}{2}\,(3-F) \qquad \Delta = \frac{2\gamma + \delta}{3} \qquad \delta = \frac{F^2}{5}\,A$$
$$\text{where } A = F\,(15 - 15\,F + 6\,F^2 - F^3). \tag{72}$$

Equation 71 includes only additive, dominance and additive×additive effects - in our notation, only coefficients of the form $b_{i_m}$, $b_{i_m i_f}$, $b_{i_m j_m}$. Thus, it does not include contributions from $V_{DD}$ or $V_{AD}$ that would enter even with just two loci. The coefficients $\sigma_A^2$, $\sigma_D^2$, $\sigma_{AA}^2$ are the usual variance components, which we write as $V_A$, $V_D$, $V_{AA}$; for two alleles per locus, $i^* = V_D$. We relate the remaining quantities to our notation below.

Substituting $i^* = \sigma_D^2$, $\bar{\gamma} = \bar{f} = \bar{\Delta} = F^2$ in Eq. 71,

$$\langle V_A^* \rangle = (1 - F)\,\sigma_A^2 + 2\,(F - 3\triangle + 2\delta)\,\sigma_D^2 + 2\,(F - \gamma)\,\sigma_{ADI}^2 + 2\,(\gamma - \delta)\,\sigma_{DI}^2 + 4\,F\,(1 - F)\,\sigma_{AA}^2 . \quad (73)$$

Substituting for the identity coefficients from Eq. 72 into Eq. 71,

$$\langle V_A^* \rangle = (1 - F)\,\sigma_A^2 + \frac{2}{5} F\,(1 - F)\,(5 - 10\,F + 10\,F^2 - 5\,F^3 + F^4)\,\sigma_D^2 + F\,(1 - F)\,(2 - F)\,\sigma_{ADI}^2 + \frac{F^2}{5}\,(1 - F)\,(15 - 20\,F + 10\,F^2 - 2\,F^3)\,\sigma_{DI}^2 + 4\,F\,(1 - F)\,\sigma_{AA}^2 . \quad (74)$$

We must now relate the quantities $\sigma_D^2$, $\sigma_{ADI}^2$, $\sigma_{DI}^2$ as defined by Walsh and Lynch (1998) to our notation. Walsh and Lynch (1998) define these in terms of additive deviations of the *j*th allele at the *i*th locus, $\alpha_{ij}$, and dominance deviations $\delta_{ijk}$ between alleles *j* and *k* at the *i*th locus. The three quantities are, respectively, the variance of dominance deviation, $\sigma_D^2$; the covariance between additive and homozygous dominance deviations, $\sigma_{ADI}^2$; and the variance of homozygous dominance deviations, $\sigma_{DI}^2$:

$$\sigma_D^2 = \sum_i \sum_{j,k} p_{ij}\, p_{ik}\, \delta^2{}_{ijk},$$
$$\sigma_{ADI}^2 = 2 \sum_j p_{ij}\, \alpha_{ij}\, \delta_{ijj}, \text{ and} \quad (75)$$
$$\sigma_{DI}^2 = \sum_i \left( \left( \sum_j p_{ij}\, \delta_{ijj}^2 \right) - i_i^2 \right), \text{ where } i_i = \sum_j p_{ij}\, \delta_{ijj}$$

and $p_{ij}$ is the frequency of the *j*th allele at the *i*th locus. The expressions printed in Walsh and Lynch (1998, Ch. 3, Table 2) are incorrect in two ways. First, there is a factor of 2 in the expression for $V_{ADI}$, because additive effects of each of the two copies of the allele contribute, but there is no such factor of 2 in the expressions for $\sigma_D^2$ and $\sigma_{DI}^2$, since there is only one dominance deviation per locus. Second, the sum is over all pairs of alleles *j*, *k* in the expression for $\sigma_D^2$, not just over distinct alleles. The definitions above agree with those given by Cockerham (1984, Table 9.1).

In our notation, $\alpha_{ij} = b_{i_m}\, \zeta_{i_m\, j}$ and $\delta_{ijk} = b_{i_m\, i_f}\, \zeta_{i_m\, j}\, \zeta_{i_f\, k}$, where $\zeta_{i_m\, j}$ is the effect of allele j. We assume that genes have the same effects across the sexes, so that we can write $\alpha_{ij} = b_{i|\phi}\, \zeta_{i_m\, j}$, $\delta_{ijk} = b_{\phi|i}\, \zeta_{i_m\, j}\, \zeta_{i_f\, k}$. The two alleles are at frequencies $q_i$, $p_i$ for $X_j = 0$, 1

respectively, and the effects are $\zeta_{i_m\, j} = \zeta_{i_f\, j} = -p_i,\ +q_j$ for $X_j = 0,\ 1$ respectively. Substituting for $p_{ij}, \alpha_{ij}, \delta_{ijk}$ we have

$$\begin{aligned}
\sigma^2_{\mathrm{D}} &= \sum_{\mathrm{i}} \mathrm{b}^2_{\emptyset|\mathrm{i}}\, \mathrm{pq}^2_{\mathrm{i}}, \\
\sigma^2_{\mathrm{ADI}} &= 2 \sum_{\mathrm{j}} \mathrm{b}_{\mathrm{i}|\emptyset}\, \mathrm{b}_{\emptyset|\mathrm{i}}\, \mathrm{pq}_{\mathrm{i}}\, (\mathrm{q}_{\mathrm{i}} - \mathrm{p}_{\mathrm{i}}), \text{ and} \\
\sigma^2_{\mathrm{DI}} &= \sum_{\mathrm{i}} \mathrm{b}^2_{\emptyset|\mathrm{i}}\, \mathrm{pq}_{\mathrm{i}} - 4\, \sigma^2_{\mathrm{D}}.
\end{aligned} \tag{76}$$

Substituting these expressions into Eq. 74 gives a formula corresponding to Eq. 76, though without terms arising from associations amongst more than two genes ($b_{i_m\, j_m\, i_f}$ etc.).

## Tables

## ■ Table 1. Summary of notation

| Symbol | Meaning |
|---|---|
| Loci, contexts, and positions | |
| $i, j$ | loci |
| $U = \{i, j\ldots\}$ | a set of loci |
| $\mathbb{i} = i_m$ | a gene at locus $i$ that was inherited from the male parent (double − struck font indicates *positions* such as this) |
| $\mathbb{U} = \{\mathbb{i}, \mathbb{j}, \ldots\}$ | a set of positions |
| $\mathbb{U} \setminus \mathbb{V}$ | the set $\mathbb{U}$ with the elements of the set $\mathbb{V}$ removed; only defined when $\mathbb{V}$ is a subset of $\mathbb{U}$ |
| Summations | |
| $\sum_{\mathbb{i}\in\mathbb{U}}$ | a sum over all positions $\mathbb{i}$ in the set $\mathbb{U}$ |
| $\sum_{\mathbb{U}\subseteq\mathbb{A}}$ | a sum over all subsets $\mathbb{U}$ of the set $\mathbb{A}$, including the set $\mathbb{A}$ itself and the empty set $\emptyset$ |
| Allele frequencies and associations | |
| $X_{\mathbb{i}}$ | indicator variable that labels the allelic state of position $\mathbb{i}$ |
| $p_{\mathbb{i}}$ | reference value for position $\mathbb{i}$ |
| $\zeta_{\mathbb{i}} = X_{\mathbb{i}} - p_{\mathbb{i}}$ | deviation of an individual at position $\mathbb{i}$ from the reference value |
| $p_{\mathbb{i}} = E[X_{\mathbb{i}}]$ | frequency of allele $X_{\mathbb{i}} = 1$ at position $\mathbb{i}$ |
| $pq_{\mathbb{i}}$ | $p_{\mathbb{i}}(1 - p_{\mathbb{i}})$ |
| $pq_{\mathbb{U}} = \prod_{\mathbb{i}\in\mathbb{U}} pq_{\mathbb{i}}$ | product of allele frequencies over the set of positions $\mathbb{U}$ |
| $\zeta_{\mathbb{U}} = \prod_{\mathbb{i}\in\mathbb{U}} \zeta_{\mathbb{i}}$ | product of deviations over the set of positions $\mathbb{U}$ |
| $D_{\mathbb{U}} = E[\zeta_{\mathbb{U}}]$ | association between the set of positions $\mathbb{U}$ |
| Phenotypes | |
| $z$ | value of a phenotypic trait |
| $\bar{z}$ | trait mean |
| $\mathbb{Z}$ | set of all positions influencing trait $Z$ |
| $b_{\mathbb{U}}$ | contribution of the set of positions $\mathbb{U}$ to the phenotype z |
| Variance components | |
| $V_G$ | total genotypic variance |
| $V_A$ | additive genetic variance |
| $V_D$ | dominance variance |
| $V_{AADDD} = V_{A(2)D(3)}$ | higher − order components |
| Expectations | |
| $E[g(X_{i_m} X_{j_f})]$ | expectation over genotype frequencies |
| $\langle \Delta p_i^2 \rangle$ | expectation of $\Delta p_i^2$ over effects of random drift |
| $V_D \left\{ \left[ \frac{A}{pq} + B \right]_D \right.$ | average of $\left\{ \left[ \frac{A}{pq} + B \right] \right.$, weighted by dominance variance |

**Table 1**

■ **Table 2. Components of the expected variance in mean that contribute more than 5% at F=0.5, under the random genotype model.**

| Component | $< \Delta \bar{z}^2 >$ at F = 0.5 | $< \Delta \bar{z}^2 >$ |
|---|---|---|
| $4 \sum_i b^2_{\{i\}\|\emptyset} \langle \Delta p_i^2 \rangle$ | 0.399 | $0.799\,F$ |
| $16 \sum_{i \neq j} b^2_{\{i,j\}\|\emptyset} \langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle$ | 0.147 | $0.587\,F^2$ |
| $64 \sum_{i \neq j \neq k} b^2_{\{i,j,k\}\|\emptyset} \langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle \langle \Delta p_k^2 \rangle$ | 0.115 | $0.917\,F^3$ |
| $8 \sum_{i \neq j} b_{\{i\}\|\emptyset}\, b_{\{i\}\|\{j\}} \langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle$ | 0.087 | $0.437\,F^2 - 0.197\,F^3 + 0.052\,F^4 - 0.021\,F^5 + 0.003\,F^6$ |
| $32 \sum_{i \neq j \neq k} b_{\{i,j\}\|\emptyset}\, b_{\{i,j\}\|\{k\}} \langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle \langle \Delta p_k^2 \rangle$ | -0.072 | $-0.578\,F^3$ |
| $4 \sum_{i \neq j} b^2_{\{i\}\|\{j\}} \langle \Delta p_i^2 \rangle \langle \Delta p_j^4 \rangle$ | 0.065 | $0.717\,F^3 - 0.497\,F^4 + 0.259\,F^5 - 0.103\,F^6 + 0.017\,F^7$ |
| $\sum_i b^2_{\emptyset\|\{i\}} \left( \langle \Delta p_i^4 \rangle - \langle \Delta p_i^2 \rangle^2 \right)$ | 0.051 | $0.291\,F^2 - 0.197\,F^3 + 0.052\,F^4 - 0.021\,F^5 + 0.003\,F^6$ |

**Table 2**

## Figure legends

Figure 1. The covariance between squared fluctuations at two loci, $\frac{\langle \Delta p_i^2 \, \Delta p_j^2 \rangle}{\langle \Delta p_i^2 \rangle \, \langle \Delta p_j^2 \rangle}$, plotted against $F$, for $R = 2Nr = 0, 0.5, 1, 2, 4$ (top to bottom).

Figure 2. The ratio $\frac{\langle \prod \Delta p_i^2 \rangle}{\prod \langle \Delta p_i^2 \rangle}$ for 2, 3, 4 loci (bottom to top), plotted against $F$, for complete linkage.

Figure 3. Changes in variance components with degree of drift for a haploid population. Genotypic values were assigned randomly with $\sigma_z^2 = 1$; there are five unlinked loci, with initial allele frequencies 0.1, 0.3, 0.45, 0.6, 0.7. Dashed lines show theoretical expectations from Eq. 28 ($V_{G(k)}$ with $k = 1$ to 5 from top to bottom at right). The additive variance ($k = 1$) is shown by the thicker lines. Solid curves show the average over 100 simulations, iterating genotype frequencies for a population of 50 haploid individuals for 200 generations.

Figure 4. Variance in $\bar{z}$, plotted against $F$. The dots show the average over 1000 replicate diploid populations of size $2N = 50$, iterated for 200 generations and held at linkage equilibrium throughout. The smooth curve shows the prediction from Eq. 38 (a sum over 462 terms). The dashed curve shows the prediction based on the actual moments of allele frequency, but assuming statistical independence across loci; these are barely distinguishable. The lower straight line shows the prediction $2FV_A$ based on additive variance alone; this is the leading contribution for small $F$. The trait is determined by five loci with complete dominance; homozygous phenotypes are chosen independently from a standard normal distribution. Initial frequencies of the recessive allele were {0.1, 0.3, 0.45, 0.6, 0.7}.

Figure 5. The contributions of the separate terms in Eq. 38 to the expected variance in trait mean, plotted against inbreeding, $F$. The same genotypic values are used as in the diploid five-locus example of Fig. 4. The upper straight line shows the leading term, $2FV_A$. Components that contribute more than 7% at $F = 0.5$ are shown by thicker lines, and are tabulated in Table 2.

Figure 6. Dots show the expected additive genetic variance, averaged across 1000 replicates; parameters as for Fig. 4. This fits closely with the expected relation, from Eq. 48. Deviations are not statistically significant. The straight line shows the contribution from the additive genetic variance in the base population, $V_A(1 - F)$.

Figure 7. The average change in additive genetic variance across 1000 replicates, shown with 10 individual sample paths. Parameters are as in Fig. 4.

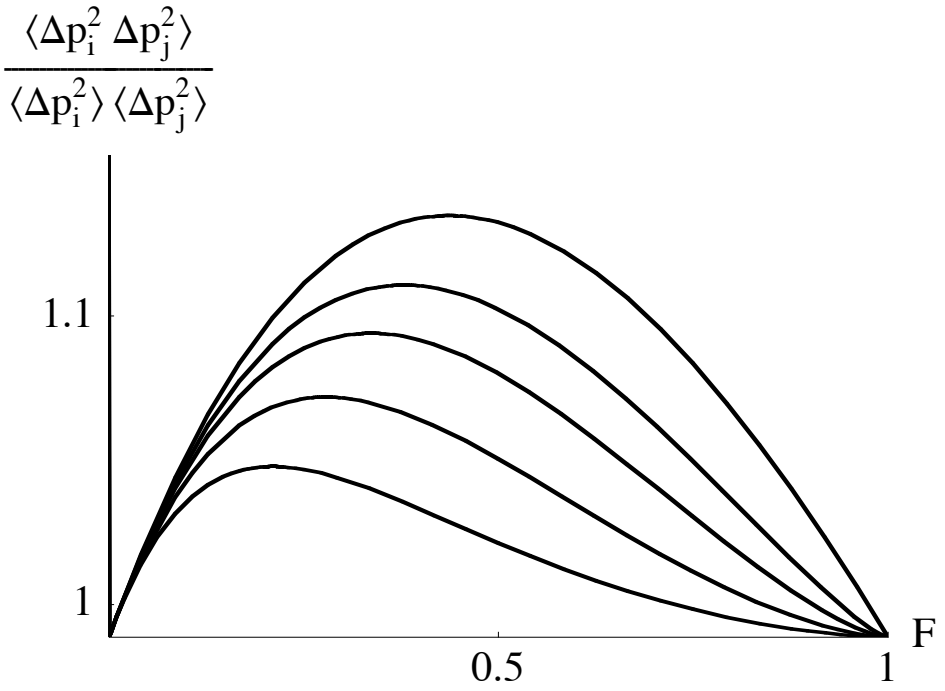
$\frac{\langle \Delta p_i^2 \, \Delta p_j^2 \rangle}{\langle \Delta p_i^2 \rangle \langle \Delta p_j^2 \rangle}$
1.1
1
0.5
1
F

**Figure 1**

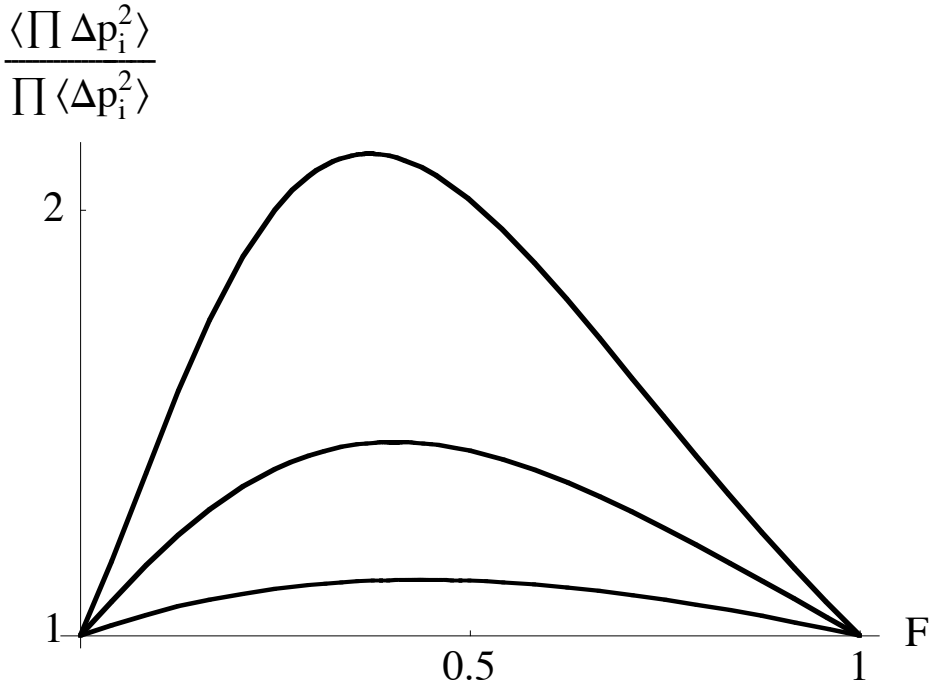
$\frac{\langle \prod \Delta p_i^2 \rangle}{\prod \langle \Delta p_i^2 \rangle}$
2
1
0.5
1
F

**Figure 2**

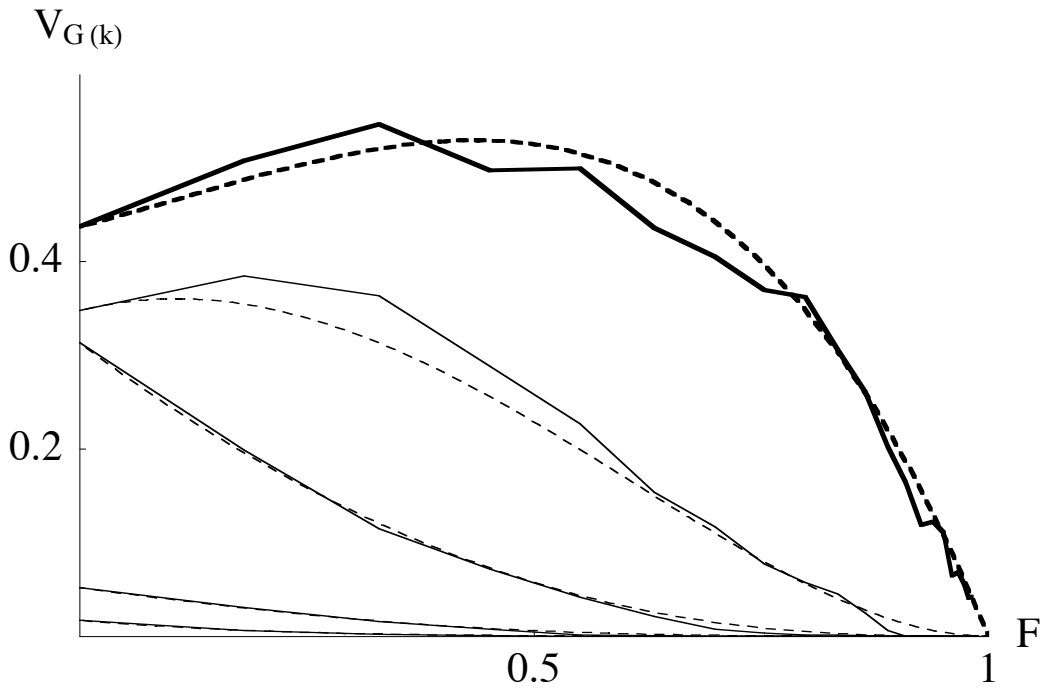


**Figure 3**

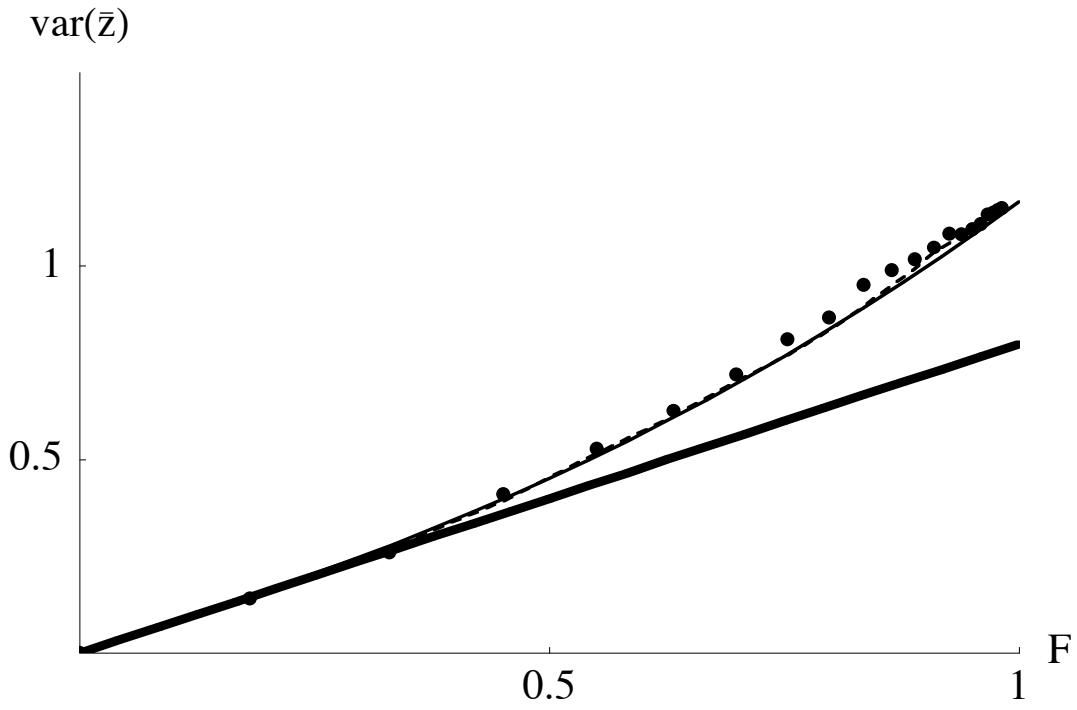


**Figure 4**

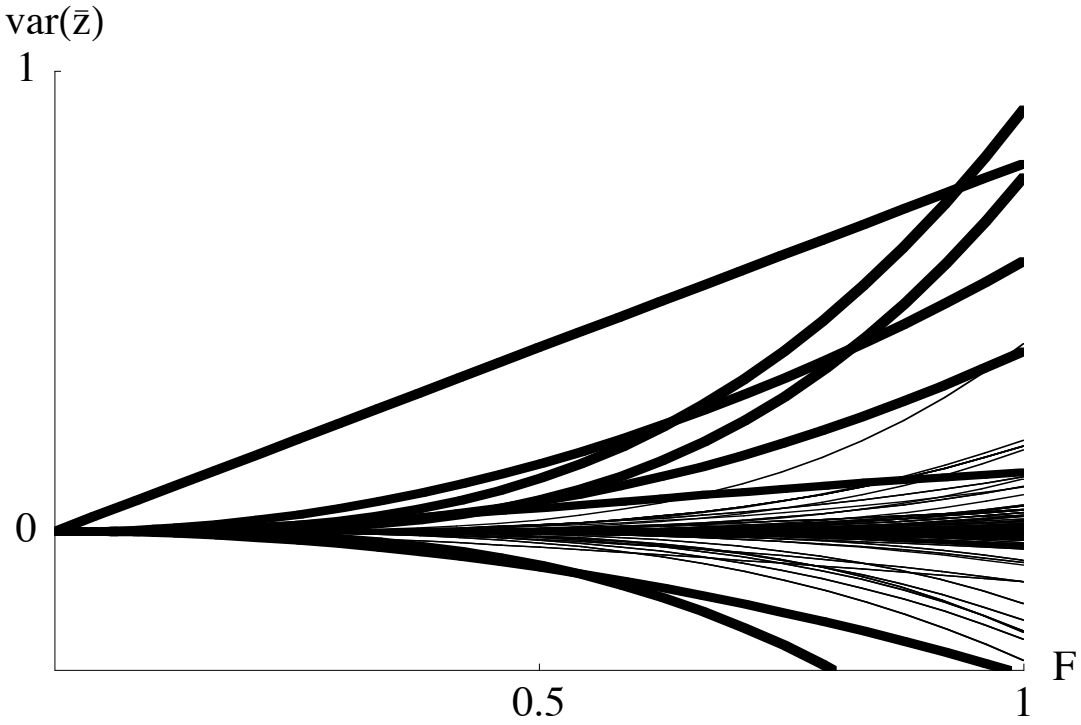


**Figure 5**

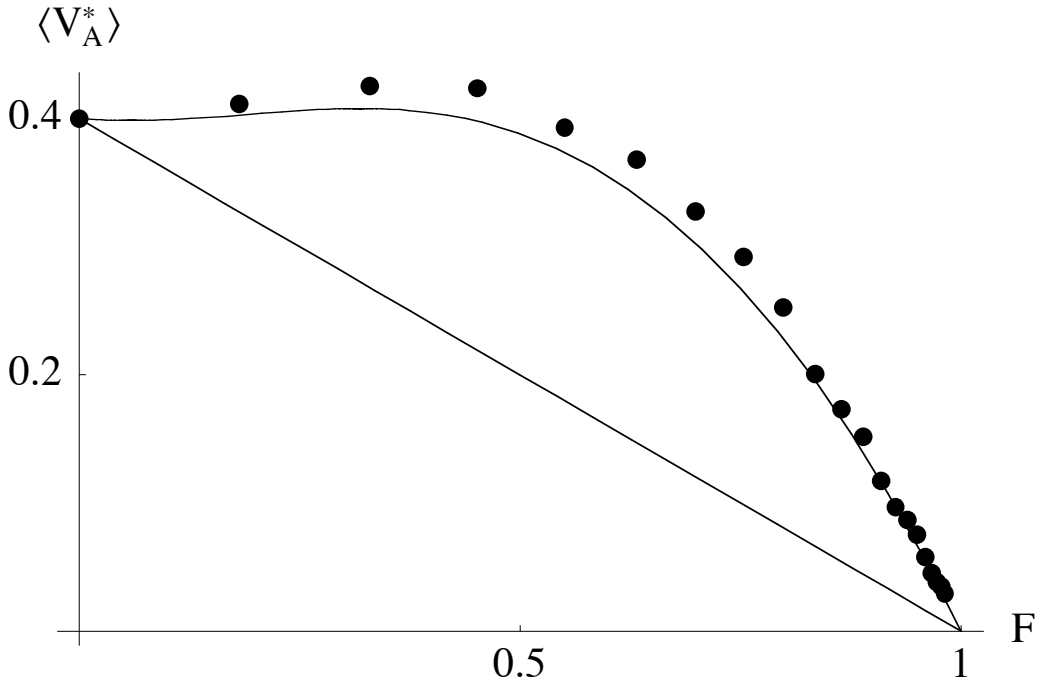


**Figure 6**

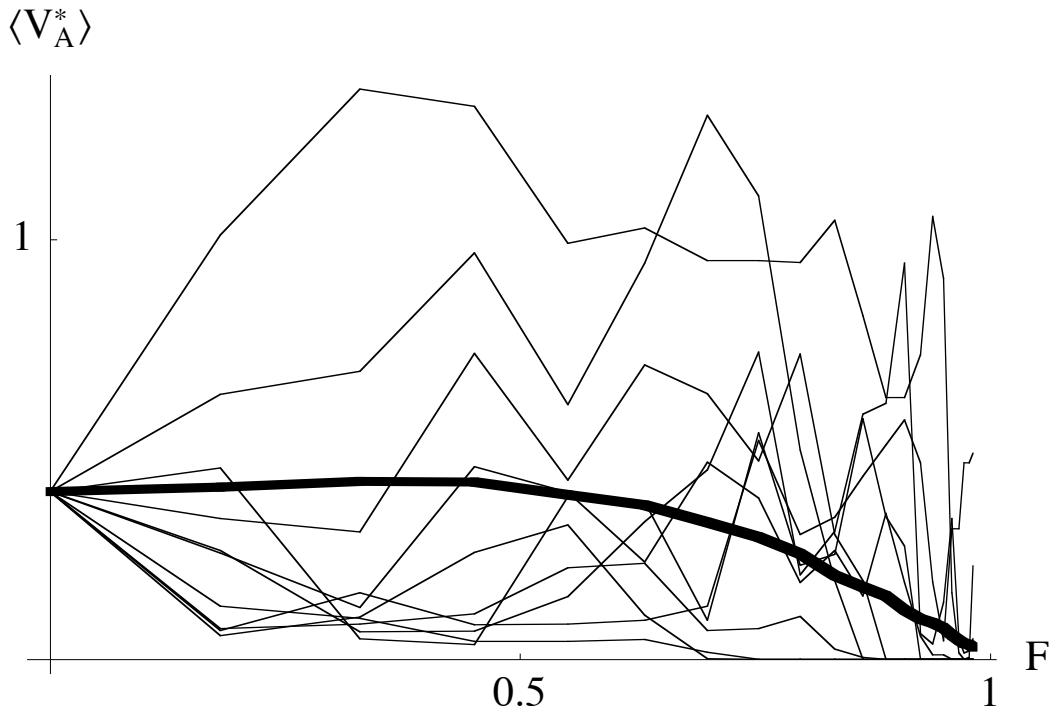


**Figure 7**