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Quantitative Variability and Multilocus Polymorphism under Epistatic Selection

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We study multilocus polymorphism under selection, using a class of fitness functions that account for additive, dominant, and pairwise additive-by-additive epistatic interactions. The dynamic equations are derived in terms of allele frequencies and disequilibria, using the notions of marginal systems and marginal fitnesses, without any approximations. Stationary values of allele frequencies and pairwise disequilibria under weak selection are calculated by regular perturbation techniques. We derive conditions for existence and stability of the multilocus polymorphic states. Using these results, we then analyze a number of models describing stabilizing selection on additive characters, with some other factors, and determine the conditions under which genetic quantitative variability is maintained.

1. INTRODUCTION

One of the most important unsolved problems of modern evolutionary theory concerns mechanisms responsible for the maintenance of high levels of genetic variability in quantitative characters observed in natural populations. If the observed variability were selectively neutral, it could be easily maintained by mutation-drift equilibrium. But the majority of quantitative characters are influenced by natural selection, predominantly, stabilizing selection (Schmalhausen, 1946; Dobzhansky, 1970). Since genetic variability of a quantitative character may be influenced by more than one locus, can stabilizing selection or a character, per se, in the absence of other factors, maintain genetic variability at several loci of the quantitative character? To answer this question, one needs to analyze complex genetic systems under selection, since simple models show elimination of genetic variability under stabilizing selection on quantitative characters (Wright, 1935; Robertson, 1956). This conclusion has stimulated further theoretical studies of the problem of maintaining the genetic variability of quantitative characters under selection. One needs more-complicated models dealing with epistatic interactions among loci.

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The mechanism investigated in the most detail is mutation-selection balance (e.g., Kimura, 1965; Bulmer, 1972; Lande, 1975, 1980; Turelli, 1984, 1988; Barton, 1986a; Burger, 1988; Gavrilets and Zhivotovsky, 1989; Barton and Turelli, 1989; Turelli and Barton, 1990; Keightley and Hill, 1990; Zhivotovsky and Gavrilets, 1990a). Although the final answer cannot be given, it seems that recurrent mutations explain only part of the observed quantitative variability (Turelli, 1984, 1988). The possibility of maintaining variability was also demonstrated with models that incorporate pleiotropy (Bulmer, 1973; Gillespie, 1984; Barton, 1990), genotype-by-environment interactions (Gillespie and Turelli, 1989), epistasis (Kojima, 1959; Gimelfarb, 1989), and unequal contributions of the loci (Nagylaki, 1989). The models of pleiotropic overdominance describe a situation in which, besides the additive contributions to the value of a quantitative trait, each heterozygous locus increases the fitness by a fixed value. The model considered by Gillespie and Turelli was constructed in such a manner that the fitness of a genotype depends only on the number of heterozygous loci (this is a special case of the symmetric models [Karlin and Feldman, 1970; Karlin, 1979; Christiansen, 1988]). Kojima found conditions for the maintenance of polymorphism at two loci under linkage equilibrium using Wright's optimum model. Gimelfarb's results are mainly numerical. Nagylaki considered special models with only two loci. Given the restrictions of these analyses, the problem of maintaining quantitative variability by means of stabilizing selection on quantitative characters, per se, is mostly open.

It should be noted that the above problem is a part of the general problem of multilocus polymorphism under selection. It is well known that selection in complex genetic systems often leads to several stable polymorphic states, in particular, having linkage disequilibrium (Karlin and Feldman, 1970). The last conclusion is important because linkage disequilibrium can influence quantitative variability and other characteristics of the population (Gallais, 1974; Bulmer, 1974; Weir *et al.*, 1980).

Numerical simulations of multilocus dynamics show that selection can produce linkage disequilibrium having some effect on the variability of quantitative characters (Lewontin, 1964; Bulmer, 1976; Zhivotovsky, 1984). The best known models that could be used to describe this effect in analytical form are models of Bulmer (1971, 1974, 1980), Lande (1975), and Turelli and Barton (1990). But these models are based on some assumptions about the phenotypic distributions and do not allow for a detailed analysis of the frequencies of genotypes. However, properties of complex genetic systems cannot be predicted a priori without knowing genetic parameters (Feldman *et al.*, 1974). Hence, it is important to know the conditions for the existence of stable multilocus polymorphisms and analytical expressions for their genotypic frequencies.

In this paper, we introduce a new class of fitness functions that can be almost completely analyzed for the existence and stability of multilocus polymorphism and that includes a number of both known and new models describing the maintenance of polygenic variability. To determine equilibria, we first transform the standard multilocus dynamic equations in terms of allele frequencies and disequilibria using a direct method for calculating induced fitnesses. We then calculate equilibrium values of allele frequencies and pairwise linkage disequilibria using regular perturbation techniques.

2. A CLASS OF FITNESS FUNCTION

Let there be two alleles at each of n loci: A_i and a_i ($i = 1, ..., n$). Let us introduce indicator variables l_i (l_i') equal to 1 or 0 if the allele at the ith locus of the paternal (maternal) gamete is A_i or a_i. Then the genotype of an individual is defined by the pair of vectors (($\boldsymbol{l}, \boldsymbol{l}'$), where $\boldsymbol{l} = (l_1, ..., l_n)$ and $\boldsymbol{l}' = (l_1', ..., l_n')$. Note that the frequency p_i of allele A_i is the mean value (over the population) of indicator variable l_i ($p_i = E\{l_i\}$, where E denotes expectation) and that linkage disequilibrium (in the sense of Slatkin (1972) between loci $i, j, ...,$ and k is $D_{ij\cdots k} = E([l_i - p_i][l_j - p_j] \cdots [l_k - p_k])$.

Let us introduce a class of fitness functions in the form of

$$w_{ll'} = \mu + \sum_i [a_i(l_i + l_i') + 2b_i l_i l_i'] + \sum_{i \neq j}\sum c_{ij}(l_i + l_i')(l_j + l_j'), \tag{1}$$

where μ, a_i, b_i, and $c_{ij} = c_{ji}$ ($i \neq j$) are constants, such that $w_{ll'} \geq 0$ for every genotype. This fitness function is the simplest generalization of the additive model to include dominance and pairwise additive-by-additive epistatic interactions. When $c_{ij} = 0$ for all i, j, Eq. (1) is reduced to that of the standard model with additivity "between" loci and dominance "within" loci. Note that Eq. (1) remains unchanged as we exchange vectors $\boldsymbol{l}$ and $\boldsymbol{l}'$ or the indicator variables l_i and l_i'. We thus assume that the effects of sex and position are absent.

In this model the mean fitness can be represented as

$$\bar{w} = \mu + \sum_i (2a_i p_i + 2b_i p_i^2) + \sum_{i \neq j}\sum c_{ij}(4p_i p_j + 2D_{ij}). \tag{2}$$

Hence the mean fitness depends only on allele frequencies and pairwise linkage disequilibria and not on linkage disequilibria of higher orders.

3. Dynamic Equations

Consider a diploid random-mating population with nonoverlapping generations. Assume that the population size is sufficiently large to ignore the effects of drift. We assume viability selection. Let $x(\mathbf{i})$ be the frequency of the $\mathbf{i}$th gamete. Then the change in the frequency of gamete $x(\mathbf{i})$ per generation (after selection and recombination) is

$$\Delta x(\mathbf{i}) = \sum_{l,l'}\sum w_{l,l'} x(l)\, x(l')\, R(l, l' \to \mathbf{i})/\bar{w} - x(\mathbf{i}), \tag{3}$$

where $R(l, l' \to \mathbf{i})$ is the probability that the individual (l, l') produces gamete $\mathbf{i}$.

For $n = 1$ or $n = 2$, Eq. (3) can be rewritten in a more conventional form. If $n = 1$, then the change in the frequency p_1 of allele A_1 per generation is

$$\Delta p_1 = (v_{A_1} - \bar{w})\, p_1/\bar{w}, \tag{4}$$

where $v_{A_1} = w_{A_1A_1} p_1 + w_{A_1a_1} q_1$ is the mean fitness of allele A_1, $q_1 = 1 - p_1$, and $w_{A_1A_1}$ and $w_{A_1a_1}$ are the fitnesses of the single-locus genotypes.

Let $n = 2$. We use a standard numeration of gametes and genotypes so that, for example, z_1, z_2, z_3, and z_4 are frequencies of gametes A_1A_2, A_1a_2, a_1A_2, and a_1a_2. Changes in gamete frequencies are described by

$$\begin{aligned}\Delta z_k = {} & (v_k - \bar{w})\, z_k/\bar{w} \\ & + \delta_k r_{12}(w_{14} z_1 z_4 - w_{23} z_2 z_3)/\bar{w} \qquad (k = 1, ..., 4),\end{aligned} \tag{5}$$

where r_{12} is the recombination fraction between loci, $v_k = \sum_h w_{kh} z_h$ is the mean fitness of gamete k, w_{kh} is the fitness of the genotype formed from gametes k and h, and $\delta_1 = \delta_4 = -1$, $\delta_2 = \delta_3 = 1$.

From Eqs. (4) and (5) one can easily derive the equation for the change in linkage disequilibrium D_{12}. Since $D_{12} = z_1 - p_1 p_2$,

$$\Delta D_{12} = \Delta z_1 - p_1\, \Delta p_2 - p_2\, \Delta p_1 - \Delta p_1\, \Delta p_2. \tag{6}$$

To study equilibria of n-locus systems ($n > 2$), we first derive dynamic equations for allele frequencies p_i and pairwise linkage disequilibria D_{ij}, using the results of Ewens and Thomson (1977).

Suppose that only m loci ($m < n$) are in fact observed. According to Ewens and Thomson, the dynamic equations for the "observed" m-locus gametes are the same as those for the genuine n-locus system, with the induced marginal fitnesses taking the place of the actual fitnesses and the induced probabilities of recombination replacing $R(l, l' \to \mathbf{i})$.

Applying this result to single-locus marginal systems, we find that changes in allele frequencies are described by

$$\Delta p_i = (v_{A_i} - \bar{w})\, p_i/\bar{w}, \tag{7}$$

where v_{A_i} is the marginal fitness of allele A_i. The corresponding equation for the change in frequency z_1, the two-locus gamete A_iA_j, is

$$\Delta z_1 = (v_{A_iA_j} - \bar{w})\, z_1/\bar{w} - r_{ij}(v_{14} z_1 z_4 - v_{23} z_2 z_3)/\bar{w}, \tag{8}$$

where $v_{A_iA_j}$ is the marginal fitness of the two-locus gamete A_iA_j, v_{14} and v_{23} are now the marginal fitnesses of the two-locus genotype (A_iA_j/a_ia_j) and (A_ia_j/a_iA_j), and r_{ij} is the recombination fraction between the ith and jth loci. Thus, to derive the dynamic equations for allele frequencies p_i and linkage disequilibria D_{ij} using Eqs. (7) and (8) and (6), we should calculate the induced fitnesses v_{A_i}, $v_{A_iA_j}$, v_{14}, and v_{23}.

4. INDUCED FITNESSES

In Appendix A, we describe a direct method for calculating induced fitnesses. The essence of the method is the consideration of induced fitnesses as the conditional means of functions of random variables l_i and l_i' (Gavrilets and Zhivotovsky, 1989; Zhivotovsky and Gavrilets, 1990a). The resulting formulas are exact and are not based on any approximations that might lead to inconsistencies in estimates of selection coefficients (Walsh, 1990).

Applying this method, we derived the following formulas for the marginal allele fitnesses,

$$v_{A_i} = \bar{w} + \left[\sum_k F_k D_{ik} + \sum_{k \neq h}\sum c_{kh} D_{ikh}\right]\Big/ p_i, \tag{9}$$

and for the induced fitness of gamete A_iA_j,

$$\begin{aligned} v_{A_iA_j} = \bar{w} + \Bigg[& p_j\left(\sum_k F_k D_{ik} + \sum_{k \neq h}\sum c_{kh} D_{ikh}\right) \\ & + p_i\left(\sum_k F_k D_{jk} + \sum_{k \neq h}\sum c_{kh} D_{jkh}\right) + \sum_k F_k D_{ijk} \\ & + \sum_{k \neq h}\sum c_{kh}(D_{ijkh} - D_{ij} D_{kh})\Bigg]\Big/ (p_i p_j + D_{ij}), \end{aligned} \tag{10}$$

where

$$F_k = a_k + 2b_k p_k + \sum_{h \neq k} 4c_{kh} p_h. \tag{11}$$

Accordingly, the difference between $v_{14} z_1 z_4$ and $v_{23} z_2 z_3$ can be represented as

$$v_{14} z_1 z_4 - v_{23} z_2 z_3 = D_{ij} \bar{w} + \sum_k F_k D_{ijk} - \sum_k 2b_k D_{ik} D_{jk}$$
$$+ \sum_{k \neq h} \sum c_{kh} (D_{ijkh} - D_{ij} D_{kh} - D_{ik} D_{jh} - D_{ih} D_{jk}). \tag{12}$$

Using this method, we can also calculate the induced fitnesses of single-locus genotypes

$$v_{A_i A_i} = \bar{w} + (2/p_i) S_{1i} + (1/p_i^2) S_{2i}, \tag{13c}$$

$$v_{A_i a_i} = \bar{w} + (1/p_i - 1/q_i) S_{1i} - (1/p_i q_i) S_{2i}, \tag{13b}$$

$$v_{a_i a_i} = \bar{w} - (2/q_i) S_{1i} + (1/q_i^2) S_{2i}, \tag{13c}$$

where

$$S_{1i} = \sum_k F_k D_{ik} + \sum_{k \neq h} \sum c_{kh} D_{ikh},$$

$$S_{2i} = \sum_k 2b_k D_{ik}^2 + \sum_{k \neq h} \sum 2c_{kh} D_{ik} D_{ih}.$$

We discuss these fitnesses below in connection with the principle of induced overdominance (Karlin, 1975; Hastings, 1982).

5. ANALYSIS

By substituting Eqs. (9)–(13) into (7) and (8) and using the relation in (6), we derive the exact dynamic equations for allele frequencies and pairwise disequilibria (Appendix A)

$$\Delta p_i = \Bigg[F_i p_i q_i + \sum_{k \neq i} F_k D_{ik}$$
$$+ 2(q_i - p_i) \sum_{k \neq i} c_{ik} D_{ik} + \sum_{k,h \neq i} \sum c_{kh} D_{ikh} \Bigg] \Big/ \bar{w}, \tag{14}$$

$$
\begin{aligned}
\Delta D_{ij} = {} & -r_{ij} D_{ij} + 2c_{ij} p_i q_i p_j q_j / \bar{w} \\
& + \Bigg(2p_i q_i \sum_{k \neq i,j} c_{ik} D_{jk} + 2p_j q_j \sum_{k \neq i,j} c_{jk} D_{ik} \Bigg) \Bigg/ \bar{w} - \Delta p_i \Delta p_j \\
& + \Bigg\{ 2[(1 - r_{ij}) c_{ij} (q_i - p_i)(q_j - p_j) + r_{ij} (b_i p_i q_i + b_j p_j q_j)] D_{ij} \\
& + (1 - r_{ij}) \Bigg[(q_i - p_i) F_i D_{ij} + (q_j - p_j) F_j D_{ij} + \sum_{k \neq i,j} F_k D_{ijk} \\
& + 2(q_i - p_i) \sum_{k \neq i,j} c_{ik} D_{ijk} + 2(q_j - p_j) \sum_{k \neq i,j} c_{kj} D_{ijk} \\
& + \sum_{k \neq h} \sum_{(k,h \neq i,j)} c_{kh} D_{ijkh} - D_{ij} \sum_{k \neq h} \sum c_{kh} D_{kh} \Bigg] \\
& + 2r_{ij} \Bigg[c_{ij} D_{ij}^2 + D_{ij} \Bigg(\sum_{k \neq i} c_{ik} D_{ik} + \sum_{k \neq j} c_{jk} D_{jk} \Bigg) \\
& + \sum_{k \neq i,j} b_k D_{ik} D_{jk} \Bigg] \Bigg\} \Bigg/ \bar{w}. \qquad (15)
\end{aligned}
$$

Note that in contrast to the more compact Eqs. (9)–(13), in Eqs. (14) and (15) we differentiate "singular" disequilibria (like D_{iij} and D_{iijj}) and nonsingular ones. "Singular" disequilibria can be found using the formulas given by Barton (1986b).

We study properties of equilibria of the model under consideration using regular perturbation techniques (see, for example, Fleming [1979] and Hastings [1986], where this approach was applied to multilocus models). Let $\mu = \mu_0 + \varepsilon\mu'$, $a_i = \varepsilon a_i'$, $b_i = \varepsilon b_i'$, $c_{ij} = \varepsilon c_{ij}'$, where ε is a small parameter and the coefficients μ_0, μ', a_i', b_i', c_{ij}' are of order one. With a larger value of ε, the effect of selection within the population is larger.

Write all unknown variables in Eqs. (14) and (15) as power series for allele frequencies

$$
p_i = p_{i,0} + \varepsilon p_{i,1} + \varepsilon^2 p_{i,2} + \cdots; \qquad (16a)
$$

and, for a typical disequilibrium coefficient of unspecified order,

$$
D = D_{,0} + \varepsilon D_{,1} + \varepsilon^2 D_{,2} + \cdots, \qquad (16b)
$$

where $p_{i,0}$ and $D_{,0}$ represent the allelic frequencies and linkage disequilibrium under random mating in the limit as selection vanishes.

Represent in a similar fashion quantities F_i:

$$\begin{aligned} F_i = {} & \varepsilon\left(a_i' + 2b_i' p_{i,0} + \sum_{k,k \neq i} 4c_{ik}' p_{k,0}\right) \\ & + \varepsilon^2\left(2b_i' p_{i,1} + \sum_{k,k \neq i} 4c_{ik}' p_{k,1}\right) + \varepsilon^3\left(2b_i' p_{i,2} + \sum_{k,k \neq i} 4c_{ik}' p_{k,2}\right) + \cdots \\ \equiv {} & \varepsilon F_{i,0} + \varepsilon^2 F_{i,1} + \varepsilon^3 F_{i,2} + \cdots, \end{aligned} \tag{16c}$$

and the mean fitness,

$$\begin{aligned} \bar{w} = {} & \mu_0 + \varepsilon\left[\sum_i p_{i,0}(a_i' + F_{i,0}) + \mu'\right] \\ & + \varepsilon^2\left[\sum_i (p_{i,1}(a_i' + F_{i,0}) + p_{i,0}F_{i,1}) + \sum_{i \neq j}\sum c_{ij} D_{ij,1}\right] + \cdots \\ \equiv {} & \bar{w}_0 + \varepsilon \bar{w}_1 + \varepsilon^2 \bar{w}_2 + \cdots. \end{aligned} \tag{16d}$$

Equilibria. At equilibrium the right-hand sides of Eqs. (14) and (15) equal zero. Myltiplying both sides of these equations by $\bar{w}$, substituting (16), and equating the terms corresponding to the same power of ε, we find algebraic equations from which perturbation terms can be easily found. In particular, we find that $D_{,0} = 0$ and that values $p_{i,0}$ are the solution of the linear algebraic system

$$p_{i,0} q_{i,0} F_{i,0} \equiv p_{i,0} q_{i,0}\left[a_i' + 2b_i' p_{i,0} + \sum_{k,k \neq i} 4c_{ik}' p_{k,0}\right] = 0. \tag{17}$$

Below, we consider equilibria with only $p_{i,0} q_{i,0} \neq 0$. The quantities $p_{i,0}$ approximate the equilibrium allele frequencies p_i with error of order ε.

The first-order perturbation for D_{ij} is

$$D_{ij,1} = 2c_{ij}' p_{i,0} q_{i,0} p_{j,0} q_{j,0} / (\mu_0 r_{ij}). \tag{18}$$

A similar result has been obtained in a number of studies (Barton, 1986b; Hastings, 1986; Turelli and Barton, 1990; Zhivotovsky and Gavrilets, 1990b). First-order perturbations for disequilibria of higher orders are equal to zero (see Appendix A).

The first-order perturbations for allele frequencies are determined as a solution of the linear equations

$$F_{i,1} p_{i,0} q_{i,0} = -2(q_{i,0} - p_{i,0}) \sum_{k \neq i} c_{ik}' D_{ik,1}. \tag{19}$$

The second-order perturbations for pairwise linkage disequilibria can be found from

$$\begin{aligned} &-r_{ij}(D_{ij,1}\bar{w}_1 + D_{ij,2}\bar{w}_0) + 2p_{i,0}q_{i,0} \sum_{k \neq i,j} c'_{ik} D_{jk,1} + 2p_{j,0}q_{j,0} \sum_{k \neq i,j} c'_{jk} D_{ik,1} \\ &\quad + 2r_{ij}(b'_i p_{i,0}q_{i,0} + b'_j p_{j,0}q_{j,0}) D_{ij,1} \\ &\quad + 2c'_{ij}[p_{i,0}q_{i,0} p_{j,1}(q_{j,0} - p_{j,0}) + p_{j,0}q_{j,0} p_{i,1}(q_{i,0} - p_{i,0}) \\ &\quad + (1 - r_{ij})(q_{i,0} - p_{i,0})(q_{j,0} - p_{j,0}) D_{ij,1}] = 0. \end{aligned} \tag{20}$$

A similar analysis of second-order terms was carried out by Zhivotovsky and Gavrilets (1990b) and Barton and Turelli (1991).

The second-order perturbations for allele frequencies can be found from

$$\begin{aligned} &F_{i,2}\, p_{i,0}q_{i,0} + F_{i,1}\, p_{i,1}(q_{i,0} - p_{i,0}) + \sum_{k \neq i} F_{k,1} D_{ik,1} \\ &\quad + 2(q_{i,0} - p_{i,0}) \sum_{k \neq i} c'_{ik} D_{ik,2} - 4p_{i,1} \sum_{k \neq i} c'_{ik} D_{ik,1} \\ &\quad + \sum_{k,h \neq i}\sum c'_{kh} D_{ikh,2} = 0. \end{aligned} \tag{21}$$

Equations (17)–(21) can be used to determine p_i and D_{ij} at polymorphic equilibria. The resulting estimates are of order ε^3. These errors can be neglected if $\varepsilon^3 \ll 1$.

6. STABILITY OF EQUILIBRIA

Now we consider an important property of the equilibria, namely, their stability. Here we deal with stability of allele frequency (16a) under weak selection only. Let $\varepsilon \to 0$. Then the allele frequency equilibria for Eq. (14) are described by (17) in the limit $p_i \to p_{i,0}$ under $\varepsilon \to 0$ (see Eq. (16a)). The dynamics of these frequencies near the stationary state can be described by the following reduced equation: $\Delta p_i = F_i p_i q_i / \bar{w}$. Let us represent it in differential form, like Crow and Kimura's (1970, p. 192) approach using weak selection,

$$dp_i/dt = p_i q_i \left[a_i + \sum_j S_{ij} p_j \right] \Big/ \bar{w}_0, \tag{22}$$

where $S_{ij} = 4c_{ij}$ $(i \neq j)$, $S_{ii} = 2b_i$. The right-hand side of (22) is equal to zero if $p_i = 0$, $p_i = 1$, or $F_i \equiv a_i + \sum_j S_{ij} p_j = 0$ (these equalities are the same as (17)). If this limiting state is asymptotically stable, then the solution of (14) is also stable for sufficiently small values of ε, since only the first term in Eq. (14), $F_i p_i q_i$, is of order ε and the others are of order ε^2 or smaller (Appendix A). Hence, from the theory of differential equations, the stability of solutions of (14) is determined by properties of (22).

We consider only isolated equilibrium states of (22). Each of these states is defined by the subdivision of the set of n loci into three subsets (Q_1, Q_2, Q_3): the loci monomorphic for alleles $a_i(Q_1)$, the loci monomorphic for alleles $A_i(Q_2)$, and the polymorphic loci (Q_3). Following Barton (1986a), denote the numbers of loci in Q_1, Q_2, and Q_3 as m, M, and v, respectively $(m+M+v=n)$. Let us define the $(n\times 1)$-vector $\mathbf{A}$ with the components $(A)_i = a_i + \sum_{j\in Q_2} S_{ij} (i=1, ..., n)$ and the $(n\times n)$-matrix $\mathbf{S}$ with the components $(\mathbf{S})_{ij} = S_{ij}$ $(i, j=1, ..., n)$. Define also the $(v\times 1)$-vector $\mathbf{A}_v$ and the $(v\times v)$-matrix $\mathbf{S}_v$ obtained from the vector $\mathbf{A}$ and the matrix $\mathbf{S}$ after deleting the rows and columns corresponding to $i, j\in Q_1\cup Q_2$.

In Appendix B we prove the following general result.

Result 1. The equilibrium state (Q_1, Q_2, Q_3) exists (i.e., all allele frequencies belong to the interval $[0, 1]$) and is isolated if $\det \mathbf{S}_v \neq 0$ and if, for all the components of the vector $-\mathbf{S}_v^{-1}\mathbf{A}_v$, the following inequalities are true

$$0 < (-\mathbf{S}_v^{-1}\mathbf{A}_v)_i < 1.$$

In this state the polymorphic allele frequencies p_i^*, $i\in Q_3$, are given by

$$p_i^* = (-\mathbf{S}_v^{-1}\mathbf{A}_v)_i.$$

This equilibrium state is stable if

$$F_i < 0, \text{ for } i\in Q_1, \qquad F_i > 0, \text{ for } i\in Q_2,$$

and the matrix $\mathbf{S}_v$ is negative definite.

Now consider the simplest special case of the general model (1) when contributions of all loci and all pairs of loci to the fitness are equal, i.e., when

$$a_i = a, b_i = b, c_{ij} = c, \qquad \text{for all } i, j, \tag{23}$$

where a, b, and c are constants. The following result is true.

Result 2. When the conditions in Eq. (23) hold, the number of polymorphic loci in a stable equilibrium state can be equal to only 0, 1, or n. A completely polymorphic equilibrium state (with $v=n$) exists and is stable if

$$a > 0, \qquad b < 0, \qquad -|b|/2 < c < \frac{2|b|-a}{4(n-1)}.$$

In this state the equilibrium allele frequencies are

$$p_i^* = a/[4c(1-n) - 2b].$$

The proof is given in Appendix B.

Consider now the case when the coefficients c_{ij} in (1) can be factored as

$$c_{ij} = \gamma c_i c_j, \tag{24}$$

where c_i and γ are constants. Assume that all c_i are different and that $d_i \equiv 2b_i - 4\gamma c_i^2 \neq 0$ ($d_i \neq d_j$ for all $i \neq j$). Let $d_1 > d_2 > \cdots > d_n$. Define the following quantities

$$\varphi_1 = \sum_i 4\gamma c_i^2/d_i, \qquad \varphi_2 = \sum_i 4\gamma a_i c_i/d_i, \qquad \varphi_3 = \varphi_2/(1+\varphi_1).$$

Result 3. Given the equalities in Eq. (24), the completely polymorphic equilibrium state exists if

$$0 < (\varphi_3 c_i - a_i)/d_i < 1, \qquad i = 1, ..., n.$$

In this state, equilibrium allele frequencies are

$$p_i^* = (\varphi_3 c_i - a_i)/d_i.$$

This equilibrium state is stable if the following inequalities hold:

$$\begin{array}{lll} d_1 < 0, \qquad \varphi_1 > -1, & & \text{if} \quad \gamma > 0, \\ \text{or} \begin{array}{l} d_1 < 0 \\ d_1 > 0, d_2 < 0, \varphi_1 < -1 \end{array} \Bigg\}, & & \text{if} \quad \gamma < 0. \end{array}$$

The proof is given in Appendix B.

7. QUANTITATIVE GENETIC MODELS

In this section we consider a number of models of selection on quantitative characters described by the fitness function (1).

Model I: Stabilizing Selection on One Character with Additive Genotype Values

Consider first the standard model of an additive character assuming that the contibution of allele A_i equals $\alpha_i/2$ and that the contribution of allele a_i equals $-\alpha_i/2$. In our notation

$$x = \sum_i \alpha_i (l_i + l_i' - 1) + e, \tag{25}$$

where e is a random environmental deviation with zero mean and a variance E. Describe stabilizing selection by a quadratic fitness function

$$w(x)=1-s(x-\theta)^2, \tag{26}$$

where θ is an optimum phenotype and s is the parameter measuring the intensity of selection ($s>0$). The mean fitness of the genotype (l, l') in this model is

$$w_{ll'}=1-sE-s\left[\sum_i \alpha_i(l_i+l_i'-1)-\theta\right]^2. \tag{27}$$

Let E be constant. Rewriting (27) in the form similar to (1), we define the equations expressing parameters μ, a_i, b_i, and c_{ij} in terms of the parameter of the model under consideration

$$\begin{aligned} a_i&=s\left(2\alpha_i\sum_j \alpha_j-\alpha_i^2+2\alpha_i\theta\right), \qquad b_i= -s\alpha_i^2, \\ c_{ij}&= -s\alpha_i\alpha_j, \qquad \mu=1-sE-s\left(\sum_i \alpha_i+\theta\right)^2. \end{aligned} \tag{28}$$

The form of c_{ij} suggests that inferences about equilibrium states of this model can be drawn with the help of Result 3. It is easy to see that $d_i=2s\alpha_i^2>0$ for all i, and, hence, in a stable equilibrium state, the number of polymorphic loci cannot be greater than one.

Model II: Stabilizing Selection on Multiple Additive Characters

Consider a generalization of model (25) for the case of k pleiotropically connected characters. Let the value of the jth character be defined by an additive model

$$x_j=\sum_i \alpha_{i,j}(l_i+l_i'-1)+e_j, \tag{29}$$

where $\alpha_{i,j}$ is the contribution of the ith locus to the jth character and e_j is a random independent environmental deviation with zero mean and a constant variance. Assume that quantities $\alpha_{i,j}$ can be factored as

$$\alpha_{i,j}=k_j\alpha_i, \tag{30}$$

where k_j, α_i are constants. Equality (30) means that the ratio of contributions of any two different loci to the same trait depends only on these loci and does not depend on the character under consideration.

Describe stabilizing selection by a fitness function (Tachida and Cockerham, 1988)

$$w(x_1, ..., x_k) = 1 - \sum_j s_j(x_j - \theta_j)^2, \tag{31}$$

where θ_j is a component of a vector $\boldsymbol{\theta} = (\theta_1, ..., \theta_k)$ of optimal values, $s_j > 0$. Note that the use of (31) instead of $\mathbf{w} = 1 - (\mathbf{x} - \boldsymbol{\theta})^T \mathbf{V}^{-1}(\mathbf{x} - \boldsymbol{\theta})$, where $\mathbf{x} = (x_1, ..., x_k)^T$ and $\mathbf{V}$ is a positive definite matrix, does not cause any loss of generality.

It is easy to show that in this model the parameters b_i and c_{ij} of fitness function (1) can be expressed as

$$b_i = -\xi\alpha_i^2, \qquad c_{ij} = -\xi\alpha_i\alpha_j,$$

where $\xi = \sum_m s_m k_m^2 > 0$. Thus $d_i > 0$ for all i in this model as in Model I and, hence, if (30) holds, in a stable equilibrium state the number of polymorphic loci cannot be greater than one. In general, selection on multiple characters can maintain polymorphisms at more than one locus (Hastings and Hom, 1990). Result 1 may be used to confirm the existence of such polymorphisms for certain parameter sets if $\alpha_{ij} \neq k_j\alpha_i$.

Model III: Genotype-dependent Stability of Development

Consider again stabilizing selection on an additive quantitative character (Eq. (25)–(26)), but now assume that the variance E of the random deviation e is different for different genotypes. This variance can be interpreted as a quantitative measure of the developmental sensitivity of the genotype to the heterogeneity of the environment. The assumption that genotypes are different with respect to environmental variance is also one of the simplest ways to take account of genotype-by-environment interaction.

Suppose that the dependence of E on the genotype is defined by the additive function with dominance

$$E = E_0 + \sum_i \left[\beta_i(l_i + l_i' - 1) + h_i(l_i + l_i' - 2l_i l_i')\right], \tag{32}$$

where β_i is the contribution of homozygous loci A_iA_i and h_i is the contribution of heterozygous loci A_ia_i. The contribution of homozygous loci a_ia_i equals $-\beta_i$. E_0 is a positive parameter, such that $E > 0$ for all genotypes. In this model, the mean fitness of a genotype (l, l') is defined by Eqs. (27) and (32). Assuming for simplicity that all loci have equal effects, i.e., that $\alpha_i = \alpha$, $\beta_i = \beta$, $h_i = h$, and $i = 1, ..., n$, the equations connecting the parameters of (1) with the parameters of the model under consideration are

$$\begin{aligned} a &= s\alpha^2(2n - 1 + 2\delta - T_1), \\ b &= -s\alpha^2(1 - T_2),\ c = -s\alpha^2, \end{aligned} \tag{33}$$

where $T_1 = (\beta + h)/\alpha^2$, $T_2 = h/\alpha^2$, $\delta = \theta/\alpha$.

Using Result 2, the constraints on T_1 and T_2 necessary for the maintenance of polymorphism at all loci are given by

$$\begin{aligned} T_1 &< 2n - 1 + 2\delta, \qquad T_2 < 1, \\ T_1 - 2T_2 &> 1 - 2n + 2\delta. \end{aligned} \tag{34}$$

Note that the region of stable polymorphism is "wider" than the region of overdominance in the character.

Model IV: Lerner's Model

In this section, we consider a special case of the model described above, which can be named after Lerner since it reflects Lerner's (1954) hypothesis of the increase in "developmental homeostasis" with the number (H) of heterozygous loci in the genotype. Consider an additive character (25) under stabilizing selection (26). Assume that variance E of the environmental deviation is a linear function of the number of heterozygous loci, H: $E = u_1 + u_2 H$. In our notation, $H = \sum_i (l_i + l_i' - 2l_i l_i')$. It is easy to see that this model is a special case of Model IV and that the parameters a, b, and c can be expressed by (33) with $T_1 = u_2/\alpha^2$ and $T_2 = u_2/\alpha^2$. The constraints on u_2 necessary for the maintenance of polymorphism can be obtained from (34).

Model V: "Corridor Model"

In this section we consider a model whose analogues have been investigated in the context of studies of the influence of genetic constraints on adaptive evolution (Wagner, 1984, 1988; Burger, 1986). Assume that selection acts on two pleiotropically connected quantitative characters. The first, x, is additive "within" and "between" loci as in (25), and the second, y, is additive "between" loci, but with "dominance" within loci

$$y = \sum_i [\beta_i(l_i + l_i' - 1) + h_i(l_i + l_i' - 2l_i l_i')] + e_y. \tag{35}$$

Let the character x be under stabilizing selection and the character y be under directional selection.

The easiest way to describe the directional selection is to use a linear fitness function

$$w(y) = 1 + ty, \tag{36}$$

where t is a parameter. The interaction of these two modes of selection can be described by the fitness function in the form

$$w(x, y) = [1 - s(x - \theta)^2][1 + ty],$$

which in the case of weak selection ($s, t \ll 1$) is approximated by

$$w(x, y) = 1 - s(x - \theta)^2 + ty. \tag{37}$$

It is obvious that this model has the same properties as Model III and that all the qualitative results concerning the maintenance of polymorphism remain valid. In particular, the conditions for the maintenance of variability in the symmetrical case (with $\alpha_i = \alpha$, $\beta_i = \beta$, and $h_i = h$) are given by (34) with $T_1 = -t(\beta + h)/s\alpha^2$, $T_2 = -th/s\alpha^2$.

Model VI: Stabilizing Selection and Pleiotropic Overdominance

Consider again Model I; assume that each locus contributes to a quantitative trait and that each heterozygous locus increases fitness by adding a fixed quantity t. This model accounting for overdominance was proposed by Bulmer (1973) (see also Gillespie, 1984). It is easily verified that the contribution of all n loci to the fitness caused by overdominance can be expressed as $t \sum_i (l_i + l_i' - 2l_i l_i')$ and that the general fitness may be represented by (37) with y as in (35) with $\beta_i = 0$ and $h_i = 1$. Thus, this model can be considered a special case of Model V.

Model VII: Additive Characters under Directional Selection

The simplest way to describe directional selection on a single trait is to use the linear fitness function (36). A generalization of this fitness function, which accounts for the case of multiple characters, is a quasilinear function of the form

$$w(x_1, ..., x_k) = 1 + \sum_g t_g x_g + \sum_{g \neq h} \sum t_{gh} x_g x_h,$$

where k is the number of characters, and t_g, t_{gh} are constants. Assume that values of the characters are determined by the additive model (29) with proportional contributions of the loci to the characters (Eq. (30)). It can be shown that in this case the parameters of (1) can be expressed as

$$b_i = \xi \alpha_i^2, \qquad c_{ij} = \xi \alpha_i \alpha_j,$$

where $\xi = \sum \sum_{g \neq h} t_{gh} k_g k_h$. Using Result 3, one can show that if $\varepsilon < 0$, then $d_i > 0$. If $\varepsilon > 0$, then $d_i < 0$, but the condition $\varphi_1 > -1$ is not satisfied. Hence, in stable equilibrium states, the number of polymorphic loci cannot be greater than one.

Model VIII: Epistatic Character under Directional Selection

Consider a quantitative character determined by additive, dominant, and pairwise additive-by-additive epistatic effects. In this case, the relation between the genotype value and the indicator variables l_i, l_i' is determined by a function of the form (1). Assume that the character is under directional selection, and describe this selection by a linear fitness function (36). It is obvious that in this model, under conditions stated in Results 1–3, a stable polymorphic state may exist and be stable.

8. SOME IMPLICATIONS

Induced Cis-Trans Effect

Model (1) assumes the absence of *cis–trans* effects on fitness, i.e., fitness is not changed if allelic genes are interchanged. However, for induced fitnesses, this is not true in general (Turelli, 1982). The induced *cis–trans* effects in two-locus marginal systems can be characterized by the difference between induced fitnesses v_{14} and v_{23} of two-locus marginal genotypes A_iA_j/a_ia_j and A_ia_j/a_iA_j. In general, induced *cis–trans* effects can be characterized by differences between induced fitnesses of m-locus genotypes with the same set of genes but with different distributions of these genes between paternal and maternal gametes. In our model, these effects are of order ε^2. To see this, just note that induced *cis–trans* effects are proportional in both linkage disequilibria and parameters a_i, b_i, and c_{ij}. All these quantities are of order ε, and hence, the products of these terms are of order ε^2. Thus, in our model, induced *cis–trans* effects are rather small.

Induced Overdominance

At an equilibrium of a multilocus model, the induced fitnesses of single-locus marginal genotypes often satisfy the conditions of overdominance,

$$v_{A_ia_i} > v_{A_iA_i}, v_{a_ia_i}. \tag{38}$$

Several examples of marginal underdominance found by Hastings (1982) demonstrate that this is not a general principle.

Using the estimates given above, it can be shown that at any polymorphic equilibrium $(p_i q_i \neq 0)$ the induced fitnesses of single-locus genotypes (13) can be represented as

$$\begin{aligned} v_{A_iA_i} &= \bar{w} + 2b_i q_i^2 + 0(\varepsilon^2), \qquad v_{a_ia_i} = \bar{w} + 2b_i p_i^2 + 0(\varepsilon^2), \\ v_{A_ia_i} &= \bar{w} - 2b_i q_i + 0(\varepsilon^2). \end{aligned} \tag{39}$$

We have shown elsewhere that a necessary condition for the stability of a completely polymorphic equilibrium in the symmetric case $(a_i = a,\ b_i = b,\ c_{ij} = c)$ is $b < 0$ (Result 2). Hence, in the symmetric case, inequalities (38) are true at least to the leading order; i.e., for stability of multilocus polymorphism for small ε, it is necessary for the induced fitness of a heterozygote to be large than the induced fitnesses of both homozygotes.

Effect of Disequilibrium on Quantitative Variability

It is well known that the additive variance of quantitative characters can be represented in the form $V_A + C_L$, where V_A is due to allele effects and C_L is due to linkage disequilibrium (Bulmer, 1974; Weir *et al.*, 1980). For the model (25), $V_A = \sum_i 2p_i q_i \alpha_i^2$ and $C_L = \sum \sum_{i \neq j} 2\alpha_i \alpha_j D_{ij}$. Results of a number of numerical simulations (Lewontin, 1964; Bulmer, 1976; Zhivotovsky, 1984) show that the reduction of genotypic variance due to the linkage disequilibrium generated by stabilizing selection can be significant even if selection and linkage are not extremely strong.

Let us consider expression (20) for the second approximation of linkage disequilibria. In two partial cases, this cumbersome formula is simplified. The first one corresponds to the situation when $p_{i,0} = q_{i,0}$ for all i, i.e., when genic variance reaches its maximum. In this case, first-order perturbations for allele frequencies are defined as a solution of a linear system $F_{i,1} = 0$ and hence $p_{k,1} = 0$ for all i (see the definition of $F_{i,1}$ in (16c) and (19)). Accordingly, it follows from (20) that

$$\begin{aligned} D_{ij,2} = {} & -D_{ij,1}[\bar{w}_1 - 2(b'_i p_{i,0} q_{i,0} + b'_j p_{j,0} q_{j,0})]/\bar{w}_0 \\ & + [2p_{i,0} q_{i,0} \sum_{k \neq i,j} c'_{ik} D_{jk,1} \\ & + 2p_{j,0} q_{j,0} \sum_{k \neq i,j} c'_{jk} D_{ik,1}]/(\bar{w}_0 r_{ij}). \end{aligned} \tag{40}$$

Similar simplifications occur when the number of loci is large (with c'_{ij} of order $1/n$ in order to fix $p_{i,0}$ as $n \to \infty$). In this case, $D_{ij,1}$ are of order $1/n$ (see (18)), the right part of (19) has the same order, and hence $p_{i,1}$ are of order $1/n$. Therefore, the last terms in (20) can be neglected in comparison with the others, and we arrive at Eq. (40). Since $D_{ij} = \varepsilon D_{ij,1} + \varepsilon^2 D_{ij,2} + 0(\varepsilon^3)$, using (18) and (40), in both these cases,

$$\begin{aligned} D_{ij} = {} & -(\varepsilon \bar{w}_1)(\varepsilon D_{ij,1})/\bar{w}_0 + 2(\varepsilon c'_{ij})\, p_{i,0} q_{i,0} p_{j,0} q_{j,0}/(\bar{w}_0 r_{ij}) \\ & + \left[2p_{i,0} q_{i,0} \sum_{k \neq i,j} (\varepsilon c'_{ik})(\varepsilon D_{jk,1}) \right. \\ & \left. + 2p_{j,0} q_{j,0} \sum_{k \neq i,j} (\varepsilon c'_{jk})(\varepsilon D_{ik,1}) \right] \Big/ (\bar{w}_0 r_{ij}) \\ & + 2[(\varepsilon b'_i)\, p_{i,0} q_{i,0} + (\varepsilon b'_j)\, p_{j,0} q_{j,0}](\varepsilon D_{ij,1})/\bar{w}_0 + 0(\varepsilon^3). \end{aligned}$$

Substitute now D_{ij} for $\varepsilon D_{ij,1}$ and p_i for $p_{i,0}$. The error due to this transformation is of order ε^3. Then, transfer the first term of the right-hand side into the left side and substitute $\bar{w}$ for the multiplier $(\bar{w}_0 + \varepsilon \bar{w}_i)$ of D_{ij}. Multiplying the resulting equality by $\bar{w}_0$ and writing c_{ij} instead of $\varepsilon c'_{ij}$, we find that with an error of order ε^3, the following equality is true:

$$\begin{aligned} D_{ij} \bar{w} = {} & \left(2c_{ij} p_i q_i p_j q_j + 2p_i q_i \sum_{k \neq i,j} c_{ik} D_{jk} + 2p_j q_j \sum_{k \neq i,j} c_{jk} D_{ik} \right) \Big/ r_{ij} \qquad (41) \\ & + 2(b_i p_i q_i + b_j p_j q_j)\, D_{ij}. \end{aligned}$$

We use this equation to compare our estimates and those of Bulmer. Consider Bulmer's model of an additive quantitative character under stabilizing selection described by Eqs. (25) and (26). The stationary state in this model is unstable (Results 2 and 3 and Model I), but it should be noted that the allele frequencies can be almost unchanged for a long time (Lewontin, 1964; Nagylaki, 1976; Gavrilets and Zhivotovsky, 1989; Zhivotovsky and Gavrilets, 1990a; Turelli and Barton, 1990). Assume that all frequencies are equal ($p_i = p$) and let allele effects also be equal ($\alpha_i = \alpha$). Note that in this model $b_i = -s\alpha^2$, $c_{ij} = -s\alpha^2$. Now multiply both sides of (41) by $2\alpha^2$ and sum over all combinations of i and j. If we neglect the contribution of the last term in (41), then the resulting equation can be approximated by

$$r_h \bar{w} C_L = -s(V_g^2 + 2V_g C_L), \qquad (42)$$

where r_h is the harmonic-mean recombination rate. This equation demonstrates that quantitative genetic variability is reduced under stabilizing selection.

Equation (42) is very similar to the equation derived by Bulmer (1974, Eq. (12)) for the case of a quadratic fitness function using the infinitesimal model and regression arguments. The only difference is the absence of the term $-sC_L^2$ from the right-hand side of (42). The obvious next step in describing the effects of disequilibrium is calculating third-order perturbations. It seems that in the cases considered in this section ($n \rightarrow \infty$ or $p_i = 0.5$), the incorporation in the analysis of third-order terms would result in an equation for C_L of the form (42), with additional terms on the right-side proportional to sC_L^2. It suggests that the analysis of third-order terms is important and perhaps would be sufficient in most cases.

But it should be concluded that Bulmer's equation is true only for extremely restricted models (additive characters, equal "weights" of the loci, equal allele frequencies, unstable polymorphic state). In other situations, exact genetic models have to be considered to describe selection on quantitative characters. For instance, quadratic selection (26) on additive characters (25) leads to Eqs. (14) and (15).

9. CONCLUSION

Our results show that a simple and obvious generalization of a standard additive model that accounts for pairwise additive-by-additive epistasis considerably weakens the conditions necessary for protected polymorphisms. In particular, overdominance per se is no longer necessary. This general approach makes it possible to study a number of quantitative genetic models describing both stabilizing selection on an additive character and various additional factors. First, we have considered stabilizing selection on an additive character with unequal contributions by different loci. We have shown that at the stable state, the number of polymorphic loci cannot be greater than one. This generalizes the results obtained for the case of equal contributions of loci (e.g., Barton, 1986a). The assumption that stabilizing selection acts not on a single character but on multiple pleiotropic traits with proportional contributions by different loci (Model II) also does not lead to stable polymorphic equilibria at more than one locus. Note, however, that Gimelfarb's (1986) and Hastings and Hom's (1990) results suggest that, in the case when contributions of different loci are not proportional, such equilibria can be expected. Result 1 may be used to find these equilibria.

A polymorphism can be protected if the environment is heterogeneous and if genotypes differ in their sensitivity to environmental conditions, i.e., if there is genotype–environment interaction in this sense (Models III and IV). In these models, we used the environmental variance E as a characteristic of such sensitivity. In Model III, the variance E is taken to be a quantitative character with some degree of dominance. In Model IV, it is assumed that E depends only on the number of heterozygous loci. This is a formalization of Lerner's (1954) hypothesis of increased "development homeostasis" in multilocus heterozygotes. Similar conclusions about the possibility of maintaining variability in the presence of genotype–environment interaction were obtained on the basis of numerical simulation (Lewontin, 1964) and by analytical methods (Gillespie and Turelli, 1989). It should be emphasized that our Models III and IV are more general than that of Gillespie and Turelli, because the former account for contributions to fitness attributable to deviations of the character from the optimum.

Another new model with stable polymorphic states is the "corridor" model (Model V). In this model, stabilizing selection on an additive trait acts simultaneously with directional selection on another character pleiotropically connected with first. Analogous models have been studied intensively in the context of investigations of the influence of genetic constraints on adaptive evolution (Wagner, 1984, 1988; Burger, 1986). Unlike these, in our models the basic state variables are allele frequencies and not the moments of phenotypic distributions. This property allows us to avoid assumptions concerning the phenotypic distributions (such as normality and constancy of covariance matrices), the validity of which, generally speaking, must be verified.

The main accomplishments of this paper, we believe, are the new models in quantitative genetics, the conditions of existence and stability of multilocus polymorphism under additive-by-additive epistatic selection including stabilizing selection on additive characters, exact formulas for the induced fitnesses that are not based on any approximations (some approximations can lead to inconsistencies in estimates of selection coefficients (Walsh, 1990)), and the second-order estimates of allele frequencies and pairwise linkage disequilibria. The estimates of allele frequencies and pairwise disequilibria presented above describe equilibria of genetic systems with an arbitrary number of loci and do not use any symmetry constraints on locus contributions. Although our dynamic equations appear less general than those of Turelli and Barton (1990) because of the special form of our fitness function (1), our model, unlike theirs, allows us to directly calculate allele frequencies and pairwise linkage disequilibria, to formulate the conditions of stability of multilocus polymorphism, and to investigate more thoroughly the influence of selection on quantitative genetic variability.

APPENDIX A

Define some subset S_m containing m elements of the set $I = \{1, ..., n\}$ of n loci. Then, as in Section 2, the m-locus gamete $C(C')$ is defined by values $l_{g,C}(l_{g,C'})$ of corresponding indicator variables, $g \in S_m$. Here we derive general formulas for induced fitnesses $v_{C,C'}$ and v_C of the m-locus genotype (C, C') and m-locus gamete C.

The fitness function (1) can be considered as a partial case of a more general fitness function,

$$w_{ll'} = \sum \gamma_{A,B}(\pi_{g\in A} l_g \pi_{g\in B} l'_g + \pi_{g\in B} l_g \pi_{g\in A} l'_g), \tag{A1}$$

where γ and π are some given functions of subsets, the summing is over all $A, B \in S$, and S is a set of all subsets of set I. As in the case for fitness function (1), in (A1) it is assumed that the effects of sex and *cis–trans* effects are absent.

The induced fitness $v_{C,C'}$ of the genotype formed by the m-locus gametes C and C' is obtained by averaging over all genotypic combinations making up these two m-locus gametes, weighted appropriately by fitnesses and frequencies. This fitness can be considered the conditional mean of random variable (A1),

$$v_{C,C'} = E\{w_{l,l'} \mid l_g = l_{g,C};\, l'_g = l'_{g,C'},\, g\in S_m\}, \tag{A2}$$

where E is the expectation operator.

Consider some term of sum (A1)

$$w_{A,B} = \gamma_{A,B}(\pi_{g\in A} l_g \pi_{g\in B} l'_g + \pi_{g\in B} l_g \pi_{g\in A} l'_g). \tag{A3}$$

Because of the independence of l_i and l'_j (owing to the randomness of matings), the contribution of this term to the mean fitness of the population is

$$\bar{w}_{A,B} = 2\gamma_{A,B} E\{\pi_{g\in A} l_g\}\; E\{\pi_{g\in B} l_g\} = 2\gamma_{A,B} z_A z_B, \tag{A4}$$

where $z_A \equiv E\{l_g = 1,\, g\in A\} = E\{\pi_{g\in A} l_g\}$ is the marginal frequency of the m-locus gamete, such that $l_g = 1$ as $g\in A$.

The contribution of (A3) to the induced fitness (A2) can be represented as

$$\begin{aligned} v_{A,B} = \gamma_{A,B}(&E\{\pi_{g\in A} l_g \mid C\}\; E\{\pi_{g\in B} l'_g \mid C'\} \\ &+ E\{\pi_{g\in B} l_g \mid C\}\; E\{\pi_{g\in A} l'_g \mid C'\}), \end{aligned} \tag{A5}$$

where we use a shorter notation for conditional means, e.g.,

$$E\{\pi_{g\in A} l_g \mid C\} = E\{\pi_{g\in A} l_g \mid l_g = l_{g,C};\, g\in S_m\}.$$

By the definition of conditional mean,

$$E\{\pi_{g\in A} l_g \mid C\} = (E\{l_g = 1,\, g\in A \text{ and } l_g = l_{g,C},\, g\in S_m\})/z_C. \tag{A6}$$

Let us define an analogue of pairwise linkage disequilibrium:

$$D_{A,C} = E\{l_g = 1,\ g \in A \text{ and } l_g = l_{g,C},\ g \in S_m\} - z_A z_C. \tag{A7}$$

Using this variable and equality (A4), the induced fitness (A2) can be written as

$$\begin{aligned} v_{C,C'} = \bar{w} + \sum \gamma_{A,B} [& (z_A D_{B,C} + z_B D_{A,C})/z_C \\ & + (z_A D_{B,C'} + z_B D_{A,C'})/z_{C'} \\ & + (D_{A,C} D_{B,C'} + D_{A,C'} D_{B,C})/z_C z_{C'}]. \end{aligned} \tag{A8}$$

Accordingly, the induced fitness of m-locus gamete C is

$$v_C = \bar{w} + \sum \gamma_{A,B} (z_A D_{B,C} + z_B D_{A,C})/z_C. \tag{A9}$$

In fitness function (1), one can distinguish four different types of terms (A3). In the first case, set A consists of a single locus ($A = k$), set B is empty ($B = 0$), $\gamma_{A,B} = a_k$, $z_A = p_k$, $z_B = 1$, $D_{A,C} = D_{k,C}$, and $D_{B,C} = 0$. The contribution of these terms to $v_{C,C'}$ is

$$\sum_k a_k (D_{k,C}/z_C + D_{k,C'}/z_{C'}).$$

In the second case, $A = B = k$, $\gamma_{A,B} = b_k$, $z_A = p_k$, $z_B = p_k$, $D_{A,C} = D_{k,C}$, $D_{B,C} = D_{k,C}$, and the contribution is

$$\sum_k 2b_k (p_k D_{k,C}/z_C + p_k D_{k,C'}/z_{C'} + D_{k,C} D_{k,C'}/z_C z_{C'}).$$

In the third case, set A consists of two different loci ($A = kh$), set B is empty, $\gamma_{A,B} = c_{kh}$, $z_A = p_k p_h + D_{kh}$, $z_B = 1$, $D_{A,C} = D_{kh,C}$, $D_{B,C} = 0$, and the contribution of these terms can be represented as

$$\begin{aligned} \sum_{k \neq h}\sum c_{kh} \{ & (p_k D_{h,C} + p_h D_{k,C} + D_{k,h,C})/z_C \\ & + (p_k D_{h,C'} + p_h D_{k,C'} + D_{k,h,C'})/z_{C'} \}, \end{aligned}$$

where $D_{k,h,C}$ is an analogue of the disequilibrium among three loci

$$\begin{aligned} D_{A,B,C} = {} & E\{l_g = 1,\ g \in A \text{ and } l_g = 1,\ g \in B \text{ and } l_g = l_{g,C},\ g \in S_m\} \\ & - z_A D_{B,C} - z_B D_{A,C} - z_C D_{A,B} - z_A z_B z_C. \end{aligned} \tag{A10}$$

Finally, in the fourth case, $A=k$, $B=h$ $(k\neq h)$, $\gamma_{A,B}=c_{kh}$, $z_A=p_k$, $z_B=p_h$, $D_{A,C}=D_{k,C}$, $D_{B,C}=D_{h,C}$, and the contribution is

$$\sum_{k\neq h}\sum c_{kh}\{(p_k D_{h,C}+p_h D_{k,C})/z_C+(p_k D_{h,C'}+p_h D_{k,C'})/z_{C'}$$
$$+(D_{k,C} D_{h,C'}+D_{k,C'} D_{h,C})/z_C z_{C'}\}.$$

These enable us to represent the induced fitness of the m-locus genotype (C, C') as

$$\begin{aligned} v_{C,C'}=\bar{w}&+\Big\{\sum_k F_k D_{k,C}+\sum_{k\neq h}\sum c_{kh} D_{k,h,C}\Big\}\Big/z_C\\ &+\Big\{\sum_k F_k D_{k,C'}+\sum_{k\neq h}\sum c_{kh} D_{k,h,C'}\Big\}\Big/z_{C'}\\ &+\Big\{\sum_k 2b_k D_{k,C} D_{k,C'}+\sum_{k\neq h}\sum c_{kh}\\ &\times(D_{k,C} D_{h,C'}+D_{k,C'} D_{h,C})\Big\}\Big/z_C z_{C'}. \end{aligned} \tag{A11}$$

Accordingly, the induced fitness of the m-locus gamete C is

$$v_C=\bar{w}+\Big\{\sum_k F_k D_{k,C}+\sum_{k\neq h}\sum c_{kh} D_{k,h,C}\Big\}\Big/z_C. \tag{A12}$$

One-Locus Marginal Systems

Let set S_m consist of a single locus, e.g., the ith. Then, it follows from definitions (A7) and (A10) that

$$D_{k,C}=D_{ik},\qquad D_{k,h,C}=D_{ikh},\qquad z_C=p_i. \tag{A13}$$

After substituting these formulas into (A12) and making obvious transformations, we get Eq. (9).

Two-locus Marginal Systems

Let set S_m consist of a pair of loci, e.g., the ith and jth. Then,

$$\begin{aligned} D_{k,C}&=p_i D_{jk}+p_j D_{ik}+D_{ijk},\\ D_{k,h,C}&=p_i D_{jkh}+p_j D_{ikh}+D_{ijkh}-D_{ij} D_{kh},\\ z_C&=p_i p_j+D_{ij}, \end{aligned} \tag{A14}$$

and using these formulas we get (10). The formulas for v_{14} and v_{23} can be derived in a similar fashion.

Disequilibria of Third and Fourth Orders

The dynamic equations for allele frequencies and pairwise disequilibria have terms proportional to third- and fourth-order disequilibria. Here we show that these terms are of order ε^2 and, hence, can be neglected in our analysis, since in Eqs. (14) and (15) they are multiplied by terms of order ε. We present only qualitative arguments and do not write down the corresponding dynamic equations for D_{ijk} and D_{ijkh} because these equations are very cumbersome.

Consider a third-order disequilibrium D_{ijk} with $i \neq j \neq k$. This disequilibrium is generated by selection and is destroyed by recombination. Let z_1 be the marginal frequency of gamete $(A_i A_j A_k)$. Then the change in D_{ijk} caused by a single act of selection can be described by

$$\begin{aligned} \Delta_s D_{ijk} = \Delta_s z_1 - \{ & p_i \Delta_s D_{jk} + p_j \Delta_s D_{ik} + p_k \Delta_s D_{ij} \\ & + (p_j p_k + D_{jk}) \Delta_s p_i + (p_i p_k + D_{ik}) \Delta_s p_j \\ & + (p_i p_j + D_{ij}) \Delta_s p_k + \cdots \}, \end{aligned} \tag{A15}$$

where we omitted higher order terms like $\Delta_s p_i \Delta_s D_{jk}$, $p_i \Delta_s p_j \Delta_s p_k$, and $\Delta_s p_i \Delta_s p_j \Delta_s p_k$. This equation follows from the definition of D_{ijk}. The change in the marginal frequency z_1 is

$$\Delta_s z_1 = (v_1 - \bar{w}) z_1 / \bar{w}, \tag{A16}$$

where v_1 is the induced fitness of the three-locus gamete $(A_i A_j A_k)$, which can be calculated using (A12).

Using Eqs. (A12), (A15), and (A16), it can be shown that

$$\begin{aligned} \Delta_s D_{ijk} = \Big\{ & \sum_g F_g (D_{ijkg} - D_{ig} D_{jk} - D_{jg} D_{ik} - D_{kg} D_{ij}) \\ & + \sum_{g \neq h} \sum c_{gh} (D_{ijkgh} - D_{gh} D_{ijk} \\ & - D_{ij} D_{kgh} - D_{ik} D_{jgh} - D_{kj} D_{igh}) \Big\} \Big/ \bar{w}. \end{aligned} \tag{A17}$$

As in Eq. (15), the general change in third-order disequilibria is

$$\Delta D_{ijk} = -r_{ijk} D_{ijk} + \Delta_s D_{ijk} + \Delta_r D_{ijk}, \tag{A18}$$

where r_{ijk} is the rate of a recombination process among three loci i, j, k, $\Delta_r D_{ijk}$ denotes other terms that are due to the recombination, analogous to the terms in Eqs. (8) and (12) for pairwise disequilibria. Every term of $\Delta_s D_{ijk}$ and $\Delta_r D_{ijk}$ is the product of either F_g or c_{gh}, that are of order ε, and either pairwise disequilibria that are of order ε or higher order disequilibria.

Using a similar approach, it can be shown that analogous relationships are valid for fourth-order disequilibria. Hence, at stationarity under selection and recombination, the reduced equations for these disequilibria are

$$\begin{aligned} r_{ijk} D_{ijk} &\approx \sum \varepsilon_1 D_{ab} + \sum \varepsilon_2 D_{cde} + \sum \varepsilon_3 D_{fghu}, \\ r_{ijkl} D_{ijkl} &\approx \sum \tilde{\varepsilon}_1 D_{\tilde{a}\tilde{b}} + \sum \tilde{\varepsilon}_2 D_{\tilde{c}\tilde{d}\tilde{e}} + \sum \tilde{\varepsilon}_3 D_{\tilde{f}\tilde{g}\tilde{h}\tilde{u}}, \end{aligned} \tag{A19}$$

where ε_i and $\tilde{\varepsilon}_i$ are of order ε or smaller. One can see that third and fourth disequilibria at the stationary state are order ε^2. Therefore, their influence on pairwise disequilibria must be order ε^2 and can be neglected in Eqs. (17)–(21).

APPENDIX B

Proof of Result 1. The polymorphic allele frequencies p_i^*, $i \in Q_3$, are defined as a solution of a linear algebraic system

$$a_i + \sum_{j \in Q_2} S_{ij} + \sum_{j \in Q_3} S_{ij} p_j^* = 0, \qquad i \in Q_3. \tag{B1}$$

The conditions for the existence of polymorphic equilibria are straightforward.

The stability of the state (Q_1, Q_2, Q_3) is defined by the signs of the real parts of the eigenvalues of the $(n \times n)$ matrix $\hat{\mathbf{R}} = (\partial/\partial p_j(dp_i/dt))$ with the diagonal elements

$$\hat{R}_{ii} = \left[(q_i - p_i)\left(a_i + \sum_j S_{ij} p_j \right) + p_i q_i S_{ii} \right] \Big/ \bar{w} \tag{B2a}$$

and the nondiagonal elements

$$\hat{R}_{ij} = p_i q_i S_{ij} / \bar{w}. \tag{B2b}$$

It can be shown that the above stability conditions are equivalent to the condition that the matrix $\mathbf{R}$ with the elements

$$R_{ii} = F_i, \quad R_{ij} = 0 \qquad \text{as} \quad i \in Q_1, j \neq i, \tag{B3a}$$

$$R_{ii} = -F_i, \; R_{ij} = 0 \qquad \text{as} \quad i \in Q_2, j \neq i, \tag{B3b}$$

$$R_{ii} = S_{ii}, \quad R_{ij} = S_{ij} \qquad \text{as} \quad i \in Q_3, j \neq i \tag{B3c}$$

is negative definite.

Of the n eigenvalues of this matrix, m eigenvalues are equal to F_i ($i \in Q_1$), M eigenvalues are equal to $-F_i$ ($i \in Q_2$), and v eigenvalues coincide with the eigenvalues of matrix $\mathbf{S}_v$.

Proof of Results 2. In the symmetrical case, the polymorphic equilibrium frequencies are defined by

$$p_i^* = \frac{a + 4c \sum p_j^*}{4c - 2b}. \tag{B4}$$

Hence, the equilibrium state (m, M, v) exists and is isolated if

(i) $4c \neq 2b$,

(ii) $\operatorname{sign}(a + 4c \sum p_j) = \operatorname{sign}(4c - 2b)$,

(iii) $|a + 4c \sum p_j| < |4c - 2b|$.

The stability of this state is determined by the eigenvalues of the matrix $\mathbf{R}$ with the elements

$$\mathbf{R}_{ii} = \begin{cases} a + 4c \sum p_j,\ R_{ij} = 0 & \text{as} \quad i \in Q_1, i \neq j, \quad \text{(B5a)} \\ (4c - 2b) - \left(a + 4c \sum p_j\right),\ R_{ij} = 0, & \text{as} \quad i \in Q_2, i \neq j, \quad \text{(B5b)} \\ 2b,\ R_{ij} = 4c, & \text{as} \quad i \in Q_3, i \neq j. \quad \text{(B5c)} \end{cases}$$

These eigenvalues are

$$\lambda = \begin{cases} a + 4c \sum p_j & (m \text{ times}) \quad \text{(B6a)} \\ (4c - 2b) - \left(a + 4c \sum p_j\right) & (M \text{ times}) \quad \text{(B6b)} \\ 2b & (\text{once when } v = 1) \quad \text{(B6c)} \\ 2b - 4c & (v - 1 \text{ times when } v > 1) \quad \text{(B6d)} \\ 2b + 4c(v - 1) & (\text{once when } v > 1). \quad \text{(B6e)} \end{cases}$$

Let the state (m, M, v) with $v > 1$ and $m > 0$ and/or $M > 0$ exist; i.e., the conditions (i), (ii), and (iii) are satisfied. The necessary condition for the stability of this state is $2b - 4c < 0$. But in this case, it follows from (ii) and (iii) that (B6a) and (B6b) must be positive. Hence, the equilibrium states with $v > 1$ and $m > 0$ and/or $M > 0$ will be unstable.

Consider a completely polymorphic equilibrium state with $v = n$, $m = M = 0$. The corresponding allele frequencies can be obtained from Eq. (B4), and the conditions for existence and stability follow from (i), (ii), (iii) and (B6).

Proof of Result 3. When (24) holds, the matrix **S** has the form

$$\mathbf{S} = \mathbf{D} + 4\gamma \mathbf{c}\mathbf{c}^T, \tag{B7}$$

where **D** is a diagonal matrix with the elements $d_i = 2b_i - 4\gamma c_i^2$, $\mathbf{c} = (c_1, ..., c_n)^T$. The inverse matrix $\mathbf{S}^{-1}$ is given by the formula

$$\mathbf{S}^{-1} = \mathbf{D}^{-1} - \mathbf{D}^{-1}\mathbf{c}\mathbf{c}^T\mathbf{D}^{-1}(4\gamma/(1+\varphi_1)), \tag{B8}$$

where $\varphi_1 = 4\gamma \mathbf{c}^T \mathbf{D}^{-1}\mathbf{c} = \sum 4\gamma c_i^2/d_i$. The conditions for the existence of polymorphic states can be obtained from Result 1 and (B8).

To draw the conclusions about stability of different equilibrium states using Result 1, we must determine the eigenvalues of matrix $\mathbf{S}_v$. This matrix has the form (B7). The eigenvalues of $\mathbf{S}_v$ satisfy

$$(\mathbf{D}_v + 4\gamma \mathbf{c}_v \mathbf{c}_v^T)\, \mathbf{v} = \lambda \mathbf{v}, \tag{B9}$$

where **v** is the eigenvector. From this equation one obtains the equality

$$\mathbf{v} = (\lambda \mathbf{I} - \mathbf{D}_v)^{-1}\, 4\gamma \mathbf{c}_v(\mathbf{c}_v^T\mathbf{v}), \tag{B10}$$

where **I** is an identity matrix. Multiplying (B9) from the left by the vector $\mathbf{c}_v^T$, substituting vector **v** by (B10), and cancelling the scalar $(\mathbf{c}_v^T\mathbf{v})$, we determine after some algebra the characteristic equation for the matrix **S**:

$$\sum_{i \in Q_3} c_i^2/(\lambda - d_i) = 1/4\gamma. \tag{B11}$$

The conditions for the negativity of eigenvalues are obtained by using the function $y = \sum c_i^2/(\lambda - d_i)$ with the line $y = 1/4\gamma$ lying to the left of the ordinate.

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REFERENCES

BARTON, N. H. 1986a. The maintenance of polygenic variation through a balance between mutation and stabilizing selection, *Genet. Res.* **47**, 209–216.

BARTON, N. H. 1986b. The effect of linkage and density-dependent regulation on gene flow, *Heredity* **57**, 415–426.

BARTON, N. H. 1990. Pleiotropic models of quantitative models of quantitative variation, *Genetics* **124**, 773–782.

BARTON, N. H., AND TURELLI, M. 1989. Evolutionary quantitative genetics: how little do we know? *Ann. Rev. Genet.* **23**, 337–370.

BARTON, N. H., AND TURELLI, M. 1991. Natural and sexual selection on many loci, *Genetics* **127**, 229–255.

BULMER, M. G. 1971. The effects of selection on genetic variability, *Am. Nat.* **105**, 201–211.

BULMER, M. G. 1972. The genetic variability of polygenic characters under optimizing selection, mutation and drift, *Genet. Res.* **19**, 17–25.

BULMER, M. G. 1973. The maintenance of the genetic variability of polygenic characters by heterozygous advantage, *Genet. Res.* **22**, 9–12.

BULMER, M. G. 1974. Linkage disequilibrium and genetic variability, *Genet. Res.* **23**, 281–289.

BULMER, M. G. 1976. The effect of selection on genetic variability: a simulation study, *Genet. Res.* **28**, 101–117.

BULMER, M. G. 1980. "The Mathematical Theory of Quantitative Genetics," Clarendon Press, Oxford.

BURGER, R. 1986. Constraints for the evolution of functionally coupled characters: a non-linear analysis of a phenotypic model, *Evolution* **40**, 182–193.

BURGER, R. 1988. Mutation-selection balance and continuum of alleles models, *Math. Biosci.* **91**, 67–83.

CHRISTIANSEN, F. B. 1988. Epistasis in the multiple locus symmetric viability model, *J. Math. Biol.* **26**, 595–618.

CROW, J. F., AND KIMURA, M. 1970. "An Introduction to Population Genetics Theory," Harper & Row, New York.

DOBZHANSKY, TH. 1970. "Genetics of Evolutionary Process," Columbia Univ. Press, New York.

EWENS, W., AND THOMSON, G. 1977. Properties of equilibria in multilocus genetic system, *Genetics* **87**, 809–819.

FELDMAN, M. W., FRANKLIN, I., AND THOMSON, G. J. 1974. Selection in complex genetic systems. I. The symmetric equilibria of the three-locus symmetric viability model, *Genetics* **76**, 135–162.

FLEMING, W. H. 1979. Equilibrium distributions of continuous polygenic traits, *SIAM J. Appl. Math.* **36**, 148–168.

GALLAIS, A. 1974. Covariances between arbitrary relatives with linkage disequilibrium, *Biometrics* **30**, 429–446.

GAVRILETS, S., AND ZHIVOTOVSKY, L. A. 1989. Influence of stabilizing selection on the genotypic variance and linkage disequilibrium, *Dokl. Biol. Sci.* (*Proc. Acad. Sci. USSR*) **304**, 34–37.

GILLESPIE, J. H. 1984. Pleiotropic overdominance and the maintenance of genetic variation in polygenic characters, *Genetics* **107**, 321–330.

GILLESPIE, J. H., AND TURELLI, M. 1989. Genotype-environment interactions and the maintenance of polygenic variation, *Genetics* **121**, 129–138.

GIMELFARB, A. 1986. Additive variation maintained under stabilizing selection: a two-locus model of pleiotropy for two quantitative characters, *Genetics* **112**, 717–725.

GIMELFARB, A. 1989. Genotypic variation for a quantitative character maintained under stabilizing selection: epistasis, *Genetics* **123**, 217–227.

HASTINGS, A. 1982. Unexpected behavior in two locus genetic models: an analysis of marginal overdominance, *Genetics* **102**, 129–132.

HASTINGS, A. 1986. Multilocus population genetics with weak epistasis. II. Equilibrium properties of multilocus selection: what is the unit of selection? *Genetics* **112**, 157–171.

HASTINGS, A., AND HOM, C. L. 1990. Multiple equilibria and maintenance of additive genetic variance in a model of pleiotropy, *Evolution* **44**, 1153–1163.

KARLIN, S. 1975. General two-locus selection models: Some objectives, results and interpretations, *Theor. Popul. Biol.* **7**, 364–398.

KARLIN, S. 1979. Principles of polymorphism and epistasis for multilocus systems, *Proc. Natl. Acad. Sci. U.S.A.* **76**, 541–545.

KARLIN, S., AND FELDMAN, M. W. 1970. Linkage and selection: two-locus symmetric viability model, *Theor. Popul. Biol.* **1**, 39–71.

KEIGHTLY, P. D., AND HILL, W. G. 1990. Variation maintained in quantitative traits with mutation-selection balance: pleiotropic side-effect on fitness trait, *Proc. R. Soc. London B* **242**, 95–100.

KIMURA, M. 1965. A stochastic model concerning the maintenance of genetic variability in quantitative characters, *Proc. Natl. Acad. Sci. U.S.A.* **54**, 731–736.

KOJIMA, K. 1959. Stable equilibria for the optimum model, *Proc. Natl. Acad. Sci. U.S.A.* **45**, 989–993.

LANDE, R. 1975. The maintenance of genetic variability by mutation in a polygenic character with linked loci, *Genet. Res.* **26**, 221–235.

LANDE, R. 1980. The genetic covariance between characters maintained by pleiotropic mutations, *Genetics* **94**, 203–215.

LERNER, I. M. 1954. "Genetic Homeostasis," Wiley, New York.

LEWONTIN, R. 1964. The interaction of selection and linkage. II. Optimum models, *Genetics* **50**, 757–782.

NAGYLAKI, T. 1976. The evolution of one- and two-locus systems, *Genetics* **83**, 583–600.

NAGYLAKI, T. 1989. The maintenance of genetic variability in two-locus models of stabilizing selection, *Genetics* **122**, 235–248.

ROBERTSON, A. 1956. The effect of selection against extreme deviants based on deviation or on homozygosis, *J. Genet.* **54**, 236–248.

SCHMALHAUSEN, I. I. 1946. "Factors of Evolution: The Theory of Stabilizing Selection," Univ. of Chicago Press, Chicago, reprinted 1986.

SLATKIN, M. 1972. On treating the chromosome as the unit of selection, *Genetics* **72**, 157–168.

TACHIDA, H., AND COCKERHAM, C. C. 1988. Variance components of fitness under stabilizing selection, *Genet. Res.* **51**, 47–53.

TURELLI, M. 1982. *Cis–trans* effects induced by linkage disequilibrium, *Genetics* **102**, 807–815.

TURELLI, M. 1984. Heritable genetic variation via mutation-selection balance: Lersh's zeta meets the abdominal bristle, *Theor. Popul. Biol.* **25**, 138–193.

TURELLI, M. 1988. Population genetic models for polygenic variation and evolution, *in* "Proceedings of the Second International Conference on Quantitative Genetics" (B. S. Weir, E. J. Eisen, M. M. Goodman, and G. Namkoong, Eds.), pp. 601–618, Sinauer, Sunderland, MA.

TURELLI, M., AND BARTON, N. H. 1990. Dynamics of polygenic characters under selection, *Theor. Popul. Biol.* **38**, 1–57.

WAGNER, G. P. 1984. Coevolution of functionally constrained characters: prerequisites for adaptive versatility, *BioSystems* **17**, 51–55.

WAGNER, G. P. 1988. The influence of variation and of developmental constraints on the rate of multivariate phenotypic evolution, *J. Evol. Biol.* **1**, 45–66.

WALSH, J. B. 1990. Inconsistencies in standard approximations for selection coefficients at loci affecting a polygenic character, *J. Math. Biol.* **28**, 21–31.

WEIR, B. S., COCKERHAM, C. C., AND REYNOLDS, J. 1980. The effect of linkage and linkage disequilibrium on the covariances of noninbred relatives, *Heredity* **45**, 351–359.

WRIGHT, S. 1935. Evolution in populations in approximate equilibrium, *J. Genet.* **30**, 257–266.

ZHIVOTOVSKY, L. A. 1984. "Integration of Polygenic Systems in Populations," Nauka Publ. House, Moscow. [In Russian]

ZHIVOTOVSKY, L. A., AND GAVRILETS, S. YU. 1990a. Stabilizing selection and linkage disequilibrium, *Sov. Genet.* **26**, 118–125.

ZHIVOTOVSKY, L. A., AND GAVRILETS, S. YU. 1990b. Selection models in quantitative genetics, *in* "Proceedings of the XV Int. Biom. Conf. Budapest, Hungary (1990)," Invited papers, pp. 79–90.