Dynamics of Genetic Variability in Two-Locus Models of Stabilizing Selection

Sergey Gavrilets*,† **and Alan Hastings***,‡,§

*Division of Environmental Studies, ‡Institute for Theoretical Dynamics, §Center for Population Biology, University of California, Davis, California 95616 and †N. I. Vavilov Institute of General Genetics, 117809 GSP-1, Moscow B-333, Russia

Manuscript received September 27, 1993
Accepted for publication June 23, 1994

ABSTRACT

We study a two locus model, with additive contributions to the phenotype, to explore the dynamics of different phenotypic characteristics under stabilizing selection and recombination. We demonstrate that the interaction of selection and recombination results in constraints on the mode of phenotypic evolution. Let V_g be the genic variance of the trait and C_L be the contribution of linkage disequilibrium to the genotypic variance. We demonstrate that, independent of the initial conditions, the dynamics of the system on the plane (V_g, C_L) are typically characterized by a quick approach to a straight line with slow evolution along this line afterward. We analyze how the mode and the rate of phenotypic evolution depend on the strength of selection relative to recombination, on the form of fitness function, and the difference in allelic effect. We argue that if selection is not extremely weak relative to recombination, linkage disequilibrium generated by stabilizing selection influences the dynamics significantly. We demonstrate that under these conditions, which are plausible in nature and certainly the case in artificial stabilizing selection experiments, the model can have a polymorphic equilibrium with positive linkage disequilibrium that is stable simultaneously with monomorphic equilibria.

MOST studies of the dynamics of quantitative characters have emphasized the 'classical' case of weak selection on a character controlled by a large number of loci [reviewed in BARTON and TURELLI (1989)]. Yet, as reviewed in ORR and COYNE (1992), the evidence that quantitative characters are controlled by many loci is not compelling–the possibility that many quantitative traits are controlled by only a few loci cannot be ruled out. In this case, selection on the individual loci underlying the trait may, in fact, be quite strong, so the role of recombination may be significant. Thus, studies of multilocus models where the fitnesses are chosen to reflect a quantitative trait may be vital for understanding the behavior of natural systems.

However, the overwhelming majority of theoretical studies of the relationship between selection and recombination using multilocus population genetics models have focussed on equilibrium behavior [reviewed in HASTINGS (1989) and NAGYLAKI (1992)]. Studies of dynamics, both theoretical and experimental, may prove much more informative, especially if it cannot be assumed that systems are at equilibrium. Questions such as "How long does it take to approach an equilibrium?" and "What can be said about characteristics of the multilocus system during the transient period?" have usually not been considered. The notable exceptions are the studies by LEWONTIN (1964), NAGYLAKI (1976, 1977, 1978, 1993) and HOPPENSTEAD (1976). These questions, however, become very important if, for example, the time to reach the equilibrium is longer than the time interval during which the fitnesses can be considered as constants. For example, questions of dynamics become paramount in any attempt to relate the predictions of the genetic models to laboratory experiments studying the dynamics of quantitative characters under selection [reviewed in HILL and CABALLERO (1992)].

Modeling of dynamics has recently attracted attention in quantitative genetics (*e.g.*, WAGNER 1984; BÜRGER 1986; KIRKPATRICK and LANDE 1989; LANDE 1991; BÜRGER and LYNCH 1994). The emphasis of these studies has mainly been on the behavior of the mean values of quantitative traits while the variances (and covariances) are assumed to be constant. To justify this simplification an assumption of weak selection is invoked. However, when applying population genetics models to quantitative traits, particularly when considering experiments, the relevant circumstance is typically strong selection. Strong selection seems also to be typical in natural populations (ENDLER 1986). Our previous analysis of some selection regimes (GAVRILETS 1993; GAVRILETS and HASTINGS 1993, 1994a) has shown that qualitative and quantitative characteristics of equilibria under strong selection are quite different from those under weak selection. We may expect that the same is true with respect to the dynamics.

Several studies with direct analyses of the dynamics of the genetic variances have been published. BÜRGER (1993) has analyzed the dynamics of different phenotypic characteristics of a quantitative trait (including the genotypic variance) under directional selection. In his model all the phenotypic changes are attributed to the changes in allele frequencies, while, because of a specific form of the fitness function, recombination does not influence the dynamics and linkage disequilibrium is absent. Bulmer (1971, 1980) has developed a complementary approach based on specific assumptions about the phenotypic and genotypic distributions [see Turelli (1988) and Gavrilets and Hastings (1994b) for a multitrait generalization]. In the resulting model the change in the genotypic variance is attributed to the change in linkage disequilibrium, while, because of the assumption about a very large number of loci with small effects, the allele frequencies do not change. Chevalet (1988) generalized this approach for the case where the number of loci, alleles, as well as the population size can be finite. Nevertheless, this analysis still has two limitations. The first is that Chevalet's approach (as well as Bulmer's) describes the dynamics of unlinked loci and it is not clear how to generalize it for the case of linked loci. The second is that this approach is heavily based on the assumption of a multivariate normal distribution of the effects of the loci. This assumption, although typical in quantitative genetic models, still has to be justified (Turelli 1984).

Thus, theoretical approaches which include linkage disequilibrium, as would be generated by strong selection, and focus on dynamics rather than equilibrium behavior, are needed. In this study, we begin such a program of investigation, looking at the dynamics of stabilizing selection within the realm of two-locus models. Using a combination of approximate methods we shall obtain a quite complete picture of the dynamics, both in terms of allele frequencies and disequilibrium, as well as quantitative genetics parameters such as the mean or the variance. Our approach is also relevant to a recent emphasis on bridging the gap between multilocus population genetics and quantitative genetics (Turelli and Barton 1990). The structure of this report is as follows. In the next section, we formulate a general model of stabilizing selection on an additive trait controlled by two diallelic loci. Then we consider the case of quadratic stabilizing selection and equal contributions of loci, where the analysis is the easiest and most complete. We then generalize these results by allowing other forms for the fitness function but still assuming equal contributions of the two loci. Finally we consider cases of quadratic stabilizing selection with unequal locus contributions.

GENERAL MODEL

We begin with a description of a general model of stabilizing selection on an additive quantitative trait determined by two diallelic loci. Assume that the alleles at locus i have effects $\alpha_i/2$ and $-\alpha_i/2$, and that $\alpha_i \neq 0$. We designate the larger of the α_i as α_1 and, without loss of generality, assume that $\alpha_1 = 1$, so that α_2 is the ratio of the effects of the alleles at the two loci. Let x_1, x_2, x_3 and x_4 be the frequencies of the gametes with the effects $z_1 = (1 + \alpha_2)/2$, $z_2 = (1 - \alpha_2)/2$, $z_3 = (-1 + \alpha_2)/2$ and $z_4 = (-1 - \alpha_2)/2$ on the trait. We shall use the standard notation for these gametes: AB, Ab, aB, and ab. We assume that the fitness depends only on genotypic value so that the fitness, w_{ij}, of an individual formed by gametes i and j and having phenotype $z_{ij} = z_i + z_j$ can be represented as

$$w_{ij} = w(z_i + z_j), \tag{1}$$

where w is the fitness function. We assume that the fitness function $w(z)$ has its optimum at z_0, decreases monotonically from its optimum, and is symmetric about it, *i.e.*, $w(z - z_0) = w(z_0 - z)$; we scale $w(z)$ so that $w(z_0) = 1$. In this paper we shall assume that the optimum phenotype z_0 is zero, *i.e.*, it coincides with that of a double heterozygote. The effects of deviation of z_0 from zero on the properties of equilibria have been analyzed in previous work (Hastings and Hom 1990; Gavrilets and Hastings 1993). Let $w_i = \sum_j w_{ij}x_j$ and $\bar{w} = \sum_i w_i x_i$ be the marginal fitness of gamete i and the mean fitness of the population. The dynamics of the gamete frequencies under selection and recombination are described by the standard relations

$$\Delta x_i = \frac{w_i - \bar{w}}{\bar{w}} x_i \mp \frac{r w_{14} D}{\bar{w}}, \tag{2}$$

where r is the recombination rate, $D = x_1x_4 - x_2x_3$ is the standard linkage disequilibrium, and w_{14} is the fitness of a heterozygote at both loci, $w_{14} = w(0)$. In (2) the sign is minus for $i = 1$ and 4 and is plus for $i = 2$ and 3.

Our analysis will present results in terms of quantitative genetics parameters, such as the mean value of the trait, $\bar{z}$, the genic variance, V_g, and the contribution of the linkage disequilibrium, C_L, to the genotypic variance of the trait under selection and recombination. Let p_i be the frequency of the allele at the ith locus that increases the trait value (allele A at the first locus, and allele B at the second locus), $q_i = 1 - p_i$. Then

$$\bar{z} = \sum_i \alpha_i(p_i - q_i), \tag{3a}$$

$$V_g = \sum_i 2\alpha_i^2 p_i q_i, \tag{3b}$$

$$C_L = \sum_{i \neq j} 2\alpha_i \alpha_j D. \tag{3c}$$

The genotypic variance of the trait $G = V_g + C_L$. The genic variance V_g is the genotypic variance that the current allele frequencies would produce if the population were in linkage equilibrium. In the extreme case of no selection, V_g does not change from generation to generation, while the absolute value of C_L is reduced to zero by recombination. We will analyze the model (2) under different assumptions about the form of the fitness function, w, and the relative contribution, α_2 of the two loci to the trait.

TABLE 1

Fitness values under quadratic stabilizing selection with equal contributions of the loci and $z_0 = 0$

	BB	Bb	bb
AA	1 - 4s	1 - s	1
Aa	1 - s	1	1 - s
aa	1	1 - s	1 - 4s

DYNAMICS UNDER QUADRATIC STABILIZING SELECTION WITH EQUAL CONTRIBUTIONS OF THE LOCI

In this section we shall assume that the contributions of the loci are equal, *i.e.*, that $\alpha_2 = 1$. Let the fitness function $w(z)$ be a quadratic

$$w(z) = 1 - sz^2, \tag{4}$$

where s is the parameter measuring the strength of selection. Under quadratic stabilizing selection (4) the mean fitness of the population can be represented as $\bar{w} = 1 - s(G + \bar{z}^2)$. The fitnesses of different genotypes in this model are given in Table 1. In this case the equilibrium structure is simple: the system evolves to one of the two monomorphic equilibria corresponding to the fixation of gamete Ab or aB. What can be said about the dynamics of the phenotypic characteristics (3)?

The dynamics of the system can be elucidated because there are different timescales in the problem, even without making an assumption of weak selection. Details of our computations are in APPENDIX A. First we introduce new variables (KARLIN and FELDMAN 1970)

$$\begin{aligned} u &= x_1 - x_4, \\ v &= x_2 - x_3, \\ t &= x_1 + x_4 - x_2 - x_3. \end{aligned} \tag{5}$$

In terms of these variables the phenotypic characteristics (3) are

$$\bar{z} = 2u, \tag{6a}$$

$$V_g = 1 - u^2 - v^2, \tag{6b}$$

$$C_L = t - u^2 + v^2. \tag{6c}$$

Using these variables one can show that the change in the mean value of the trait in one generation is

$$\Delta\bar{z} = -\frac{s}{\bar{w}}\left(1 + \frac{G}{2} - \frac{\bar{z}^2}{4}\right)\bar{z}. \tag{7}$$

Here we would like to emphasize two points. The first is that this equation is *exact*. The second is that surprisingly it is quite different from the equation $\Delta\bar{z} = -(2s/\bar{w})G\bar{z}$ that one would derive from the standard formula in quantitative genetics $\Delta\bar{z} = G(\partial \ln \bar{w}/\partial\bar{z})$ (LANDE 1979).

In our model the variable u, and hence the mean of the trait $\bar{z}$, monotonically evolves to zero (HASTINGS 1987). In APPENDIX A we show that u approaches zero *quickly* and hence

$$\bar{z} \rightarrow 0 \text{ quickly}. \tag{8}$$

In other words, the evolution of the mean proceeds much faster than the evolution of other phenotypic characteristics (*cf.* BULMER 1980), so that after a short time the absolute value of the mean is extremely small, and the other phenotypic characteristics have changed little.

We then concentrate on the dynamics of V_g and C_L, under the assumption that $\bar{z} \approx 0$. Note that if the optimum value of the trait is about the population mean (a condition usually met in stabilizing selection experiments), then $\bar{z} \approx 0$ from the beginning. The changes in V_g and C_L in one generation are $\Delta V_g = -2v\Delta v - (\Delta v)^2 \approx -2v\Delta v$, and $\Delta C_L = \Delta t + 2v\Delta v + (\Delta v)^2 \approx \Delta t + 2v\Delta v$, where we have assumed that the change in v in one generation satisfies $\Delta v \ll 1$. We can now use phase-plane methods to study these dynamics (*e.g.*, CODDINGTON and LEVINSON 1955). It is useful to approximate the dynamics in this phase plane by a differential equation to simplify the analysis. The qualitative features of the dynamics are not altered by this change to continuous time. Dividing ΔC_L by ΔV_g and substituting the differential ratio dC_L/dV_g for the difference ratio $\Delta C_L/\Delta V_g$, we get the first order differential equation

$$\frac{dC_L}{dV_g} = \frac{-rC_L - \frac{1}{2}s(V_g^2 - C_L^2)}{-s(1 - V_g)(V_g + C_L)}, \tag{9}$$

that approximates the dynamics of the components of the genotypic variance on the phase-plane (V_g, C_L). Note that the variables V_g and C_L satisfy

$$0 \leq V_g \leq 1, \qquad -V_g \leq C_L \leq (1 - \sqrt{1 - V_g})^2. \tag{10}$$

The first inequality is obvious, while the second guarantees the non-negativity of the gamete frequencies at $\bar{z} = 0$. In APPENDIX B, we describe the detailed phase-plane analysis of (9), and we merely highlight some of the results here.

The most important and surprising feature of the dynamics of (9) is that in the phase-plane the system quickly evolves to a line along which the dynamics are slower (see Figure 1 and APPENDIX B). The line to which the system evolves is very close to the straight line given by the equation $C_L = \theta V_g$, where $\theta < 0$. It connects two equilibria of (9): the stable equilibrium (0,0) and the unstable equilibrium $(1, \theta)$. The former corresponds to the stable monomorphic equilibria of (2) with fixation of gamete Ab or aB. The latter corresponds to the unstable polymorphic equilibrium of (2) with allele frequencies of one half and a negative linkage disequilibrium of $D = \theta/4$. At this equilibrium the contribution of linkage disequilibrium to the genotypic variance is

$$\theta = r/s - \sqrt{(r/s)^2 + 1}. \tag{11}$$

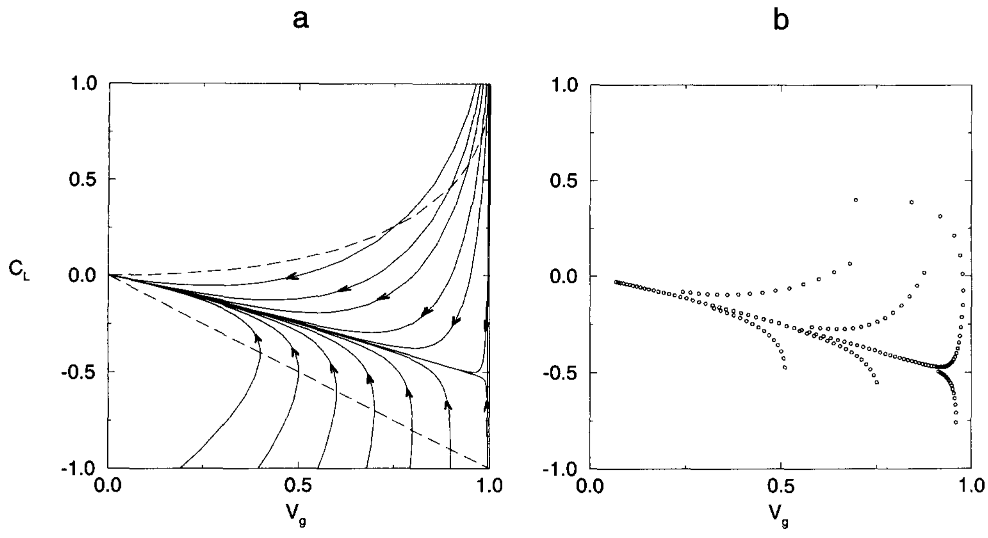

FIGURE 1.—The dynamics under quadratic stabilizing selection with equal contributions of the loci for $s = 0.15$, $r = 0.1$ and $\theta = -0.54$. (a) The phase-portrait of (9); the dashed lines indicate the phase-plane defined by (10). (b) Exact trajectories of (2) on the plane (V_g, C_L) for different initial conditions.

If selection is very weak (*i.e.*, if $s \ll r$), then $\theta \approx 0$, and the dynamics of the system correspond to that one studied by NAGYLAKI (1976, 1977, 1978, 1993) and HOPPENSTEAD (1976): there is a quick movement towards the so-called "quasi-linkage equilibrium" state with slow evolution of allele frequencies afterward. Our findings show that a similar separation of timescales takes place in general even without assuming weak selection (*cf.* CHEVALET 1988). However, the population is not at linkage equilibrium (unless $s \ll r$). In our model, the population evolves to a monomorphic state, but during the evolution it is characterized by some level of negative linkage disequilibrium. While both the genic variance V_g and the contribution of linkage disequilibrium C_L decrease, their ratio C_L/V_g is about the same as at the unstable polymorphic equilibrium. Even moderately strong selection is sufficient to produce high levels of linkage disequilibrium at this state (GAVRILETS 1993). This equilibrium is unstable but nevertheless determines the mode and as we shall see below the rate of the evolution. If one ceases selection, than we expect to observe an increase in the genotypic variance to the level of the genic variance as recombination destroys negative linkage disequilibrium. The fact that the ratio C_L/V_g does not change with time implies that the ratio of the genotypic variance after all disequilibrium was destroyed to the genotypic variance at the moment when selection stops, is independent of the time when selection was ceased (and equals $1/(1 + \theta)$).

The existence of different timescales in the model allows us to analyze the rate of evolution directly (*cf.* CHEVALET 1988). As soon as a trajectory approaches the line $C_L = \theta V_g$, we can assume that $C_L \approx \theta V_g$. Approximating the change in the genic variance in one generation ΔV_g by the derivative dV_g/dT, we get a single equation that describes how V_g changes with time T:

$$\frac{dV_g}{dT} = \frac{-SV_g(1 - V_g)}{1 - SV_g}. \tag{12}$$

where $S = s(1 + \theta)$ is a single parameter that determines the rate of evolution. Note that the denominator in the right-hand side of (12) is the mean fitness of the population evaluated at $\bar{z} = 0$ and $C_L = \theta V_g$. Equation (12) has a simple integral

$$\ln\left(\frac{V_g}{(1 - V_g)^{1-S}}\right) = -ST + c, \tag{13}$$

where c is a constant that depends on the initial conditions. One can use (13) to find the time that it takes to reach some specified level of the genic variance starting from some other specified level. Figure 2A illustrates the dependence of the rate of evolution on S. Figure 2B shows how S depends on the strength of selection s and the recombination rate r. We see that, as expected, both strong selection and loose linkage increase the rate of evolution. These Figures show that if the loci are moderately linked (say, with $r \leq 0.1$), even strong selection can require more than a hundred generations to change the genic variance significantly. Using the fact that along the line $C_L = \theta V_g$, $C_L \approx \theta V_g$, $G \approx (1 + \theta) V_g$, and $\bar{w} \approx 1 - s(1 + \theta) V_g$, we can also use Equations 12 and 13 for analyzing the dynamics of linkage disequilibrium, of the genotypic variance and of the mean fitness of the population.

OTHER MODELS OF STABILIZING SELECTION

Although our analysis is most complete in the case of equal locus contributions and quadratic selection, substantial progress is possible in the analysis of other cases.

Equal contributions of the loci, arbitrary fitness function: In this section we again assume the locus contributions are equal, but the form of fitness function is arbitrary. If $\alpha_2 = 1$, then the genotypic value can only be equal to 0, ∓ 1, ∓ 2, and the fitness function can be completely characterized using only two parameters, $\beta \equiv w(0) - w(\mp 1)$ and $\delta = w(0) - w(\mp 2)$, $\beta \leq \delta$ (Table 2). The resulting fitness model is a special case of the general symmetric model (see Table 3) studied

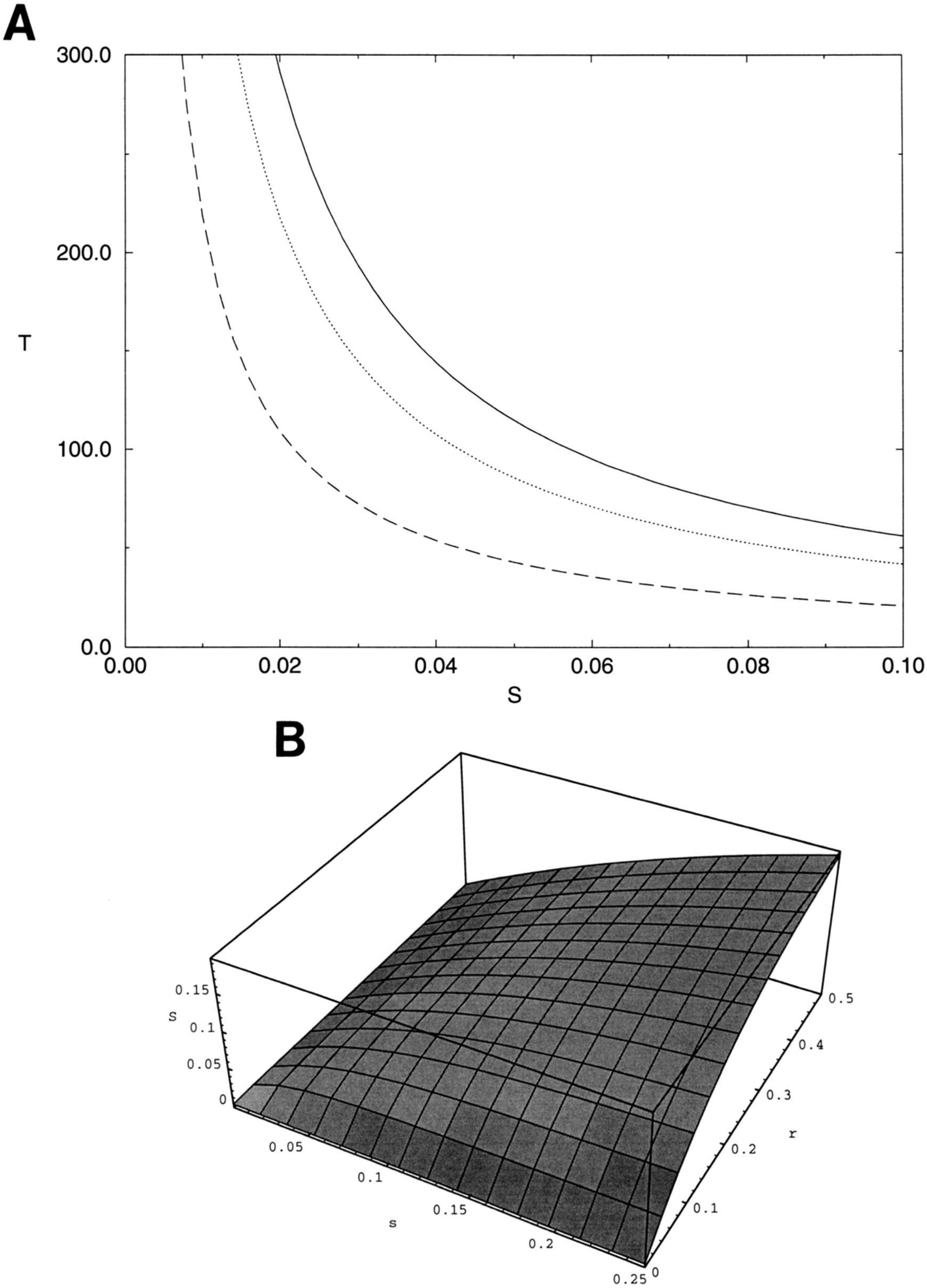

FIGURE 2.—Influence of the parameters of the model on the rate of evolution. (A) The time that it takes to change the genic variance V_g from 0.95 to 0.05, from 0.9 to 0.1, and from 0.75 to 0.25 respectively. (B) The value of S as function of the intensity of selection s and the recombination rate r.

in a number of papers (*e.g.*, BODMER and FELSENSTEIN 1967; KARLIN and FELDMAN 1970). This special case has not been analyzed in detail. The following result summarizes the properties of stable equilibria of (2) in this model.

Result 1: *If* $2\beta \leq \delta$, *then the only possible stable equilibria are fixation equilibria* $x_2 = 1$ *or* $x_3 = 1$. *If* $2\beta > \delta$ *and selection is sufficiently strong relative to linkage, then in addition to these fixation equilibria which remain stable, there exists a locally stable polymorphic*

TABLE 2

Fitness values under arbitrary symmetric stabilizing selection with equal contributions of the loci and $z_0 = 0$

	BB	Bb	bb
AA	$1 - \delta$	$1 - \beta$	1
Aa	$1 - \beta$	1	$1 - \beta$
aa	1	$1 - \beta$	$1 - \delta$

TABLE 3

Fitness values in the symmetric fitness model

	BB	Bb	bb
AA	$1 - \delta$	$1 - \beta$	$1 - \alpha$
Aa	$1 - \gamma$	1	$1 - \gamma$
aa	$1 - \alpha$	$1 - \beta$	$1 - \delta$

equilibrium with allele frequencies equal to one half and positive linkage disequilibrium.

In APPENDIX A, we present the proof of this Result and describe how the properties of the equilibria and the outcome of the evolution depend on the parameters. The stable polymorphic equilibrium whose existence was stated in Result 1 deserves to be discussed in some detail. Previously we have shown that if the contributions of the loci are different, than strong stabilizing selection can maintain variability in two (GAVRILETS and HASTINGS 1993) or many (GAVRILETS and HASTINGS 1994a) loci. Result 1 shows that the assumption about non-equal contributions of the loci is not necessary. The condition $2\beta > \delta$ means that on the plane $(z, w(z))$ the point $(1, w(1))$ lies below the straight line that connects the points $(0, 1)$ and $(2, w(2))$, *i.e.*, $w(z)$ is convex. This can be satisfied, for example, in the case of a double truncation or if $w(z)$ is a Gaussian fitness function. The polymorphic equilibrium exists simultaneously with two monomorphic equilibria and, hence, the outcome of evolution depends on the history. Contrary to what intuition about selection on a quantitative trait would suggest, this equilibrium has a large level of *positive* linkage disequilibrium, *i.e.*, there is an excess of gametes in the coupling phase. The population evolves to this equilibrium only if initially the population is characterized by a high level of positive linkage disequilibrium, *i.e.*, the gamete pool consists mainly of gametes AB and ab with a small proportion of gametes Ab and aB. Such "initial conditions" are plausible in selection experiments when the line subject to selection is produced from the initial cross of two highly inbred lines (with the genotypes AB/AB and ab/ab). In other cases the population evolves to monomorphic equilibria. A possibility of simultaneous stability of a polymorphic equilibrium and monomorphic equilibria in a different special case of the general symmetric model was demonstrated in (FELDMAN and LIBERMAN 1979).

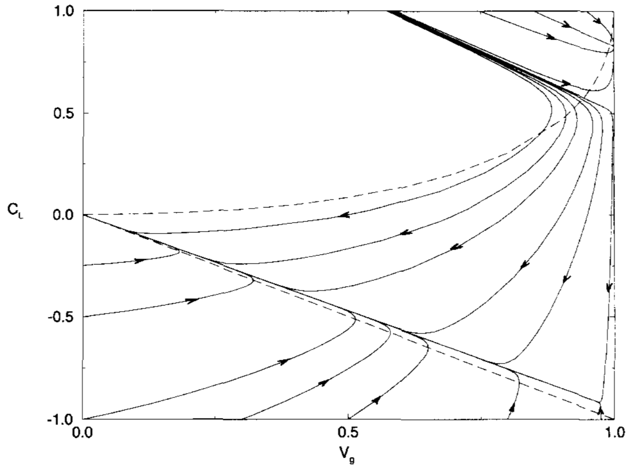

FIGURE 3.—The phase-portrait of (14) for $r = 0.01$, $\beta = 0.35$, $\delta = 0.40$. The dashed lines indicate the phase-plane defined by (10).

If the contributions of the loci to the trait are equal, the mean value of the trait $\bar{z}$ monotonically evolves to the optimum (HASTINGS 1987). One can easily derive an analog of Equation 7, which again is different from the equation that one would derive from the standard formula in quantitative genetics $\Delta\bar{z} = G(\partial \ln \bar{w}/\partial\bar{z})$. In APPENDIX A we show that $\bar{z}$ approaches zero *quickly* and that after some *short* time (typically about ten to fifteen generations) the change in the components of the genotypic variance on the phase plane (V_g, C_L) can be approximated by the first order differential equation

$$\frac{dC_L}{dV_g} \tag{14}$$

$$= \frac{-rC_L - \tfrac{1}{2}\beta(V_g^2 - C_L^2)\,[1 + (V_g + C_L)\,(\delta/4\beta - 1)]}{-\beta(1 - V_g)(V_g + C_L)\,[1 + (V_g + C_L)\,(\delta/4\beta - 1)]}.$$

As before the variables V_g and C_L must satisfy the inequality (10). The transient dynamics of the components V_g and C_L of the genotypic variance have two qualitatively different regimes. The first one corresponds to the evolution towards a polymorphic equilibrium, while the second one corresponds to the evolution towards one of the two possible monomorphic equilibria. We shall consider these regimes separately. On the phase-plane (V_g, C_L) with the variables satisfying (10) the polymorphic equilibrium, which exists and is stable if $2\beta > \delta$ and selection is sufficiently strong relative to recombination, is given by the point $(1, C_L^*)$, where $C_L^* > 0$ solves the numerator of Equation 14. The system evolves toward this state only if initially it belongs to the domain of attraction of this equilibrium. One can show (see APPENDIX B and Figure 3) that the domain of attraction of the polymorphic state is small. If the system initially belongs to this domain (that, as we have argued above, seems to be plausible in some experimental situations), we expect to observe only small changes in V_g and C_L through time.

Now let us assume that the parameter values are such that the polymorphic steady state with positive linkage

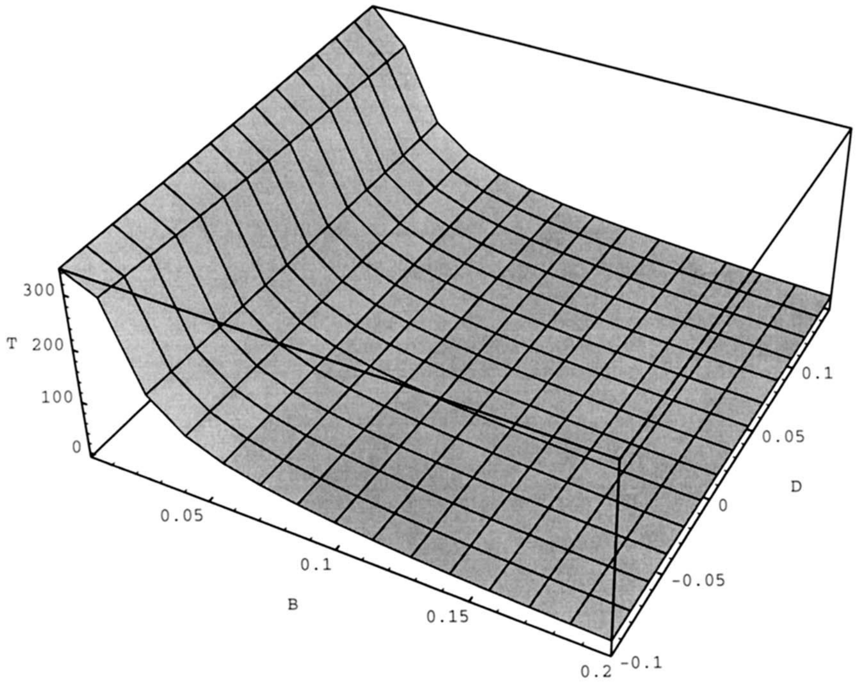

FIGURE 4.—The time that it takes to change the genic variance V_g from 0.95 to 0.05 as function of $\mathcal{B}$ and $\mathcal{D}$.

disequilibrium does not exist or that the initial conditions do not belong to its domain of attraction. In this case the dynamics of the system are similar to those in the case of quadratic stabilizing selection: the system quickly evolves to a line along which the dynamics are slower (see Figure 3 and APPENDIX B). This line is very close to the straight line $C_L = \theta V_g$, where as before θ is the contribution of linkage disequilibrium to the genotypic variance at an unstable polymorphic equilibrium with allele frequencies one half and negative linkage disequilibrium. The value $-1 \leq \theta \leq 0$ can be found as a solution of a cubic algebraic equation defined by the numerator of (14) with $V_g = 1$.

As soon as a trajectory approaches the line $C_L = \theta V_g$, we can assume that $C_L \approx \theta V_g$. Approximating the change in the genic variance in one generation ΔV_g by dV_g/dT, we get a single equation that describes how V_g changes with time T:

$$\frac{dV_g}{dT} = \frac{-\mathcal{B}V_g(1 - V_g)(1 + \mathcal{D}V_g)}{1 - \mathcal{B}V_g - \mathcal{B}\mathcal{D}V_g^2/2}. \tag{15}$$

where $\mathcal{B} = \beta(1 + \theta)$, $\mathcal{D} = (\delta/4\beta - 1)(1 + \theta)$. Note that the denominator in the right-hand side of (15) is the mean fitness of the population evaluated at $\bar{z} = 0$ and $C_L = \theta V_g$. Equation 15 has an integral

$$\frac{-1 + \mathcal{B} + \mathcal{B}\mathcal{D}/2}{1 + \mathcal{D}} \ln(1 - V_g) + \ln(V_g) - \frac{\mathcal{D} + \mathcal{B}/2}{1 + \mathcal{D}} \ln(1 + \mathcal{D}V_g) = -\mathcal{B}T + c, \tag{16}$$

where c is a constant that depends on the initial conditions. If $\delta = 4\beta$ (which is the case for quadratic stabilizing selection), then $\mathcal{D} = 0$, and Equations 15 and 16 reduce to Equations 12 and 13 correspondingly. One can use (16) to find the time that it takes to reach some specified level of the genic variance. Figure 4 illustrates the dependence of the rate of evolution on $\mathcal{B}$ and $\mathcal{D}$. One can see that the rate of evolution depends on $\mathcal{D}$ only weakly. As before, we can also use Equations 15 and 16 for analyzing the dynamics of C_L, G and $\bar{w}$.

Non-equal contributions of loci; quadratic stabilizing selection: In this section we shall assume that the contributions of the loci are different, *i.e.*, that $\alpha_2 < 1$, and that the fitness function is quadratic (4). The equilibria in this model were analyzed in GAVRILETS and HASTINGS (1993). Both equilibrium and transient behavior in this model are more complicated, but we still can get some analytical results. In APPENDIX A we show that on the phase-plane (u, v) the trajectories of the system *quickly* approach the line $u = -kv$, where k is a positive value that depends on the parameters of the model. This implies that on the phase-plane (p_1, p_2) the trajectories of the system *quickly* approach a straight line that passes through the point (½, ½). On the phase-plane $(\bar{z}, V_g)$ the trajectories of the system *quickly* approach the curve

$$V_g = \frac{1 + \alpha_2^2}{2} - K\bar{z}^2, \tag{17a}$$

where K, which is positive, depends on k and α_2. Along this curve

$$\frac{V_{1,\max} - V_{g,1}}{V_{2,\max} - V_{g,2}} = \text{const}, \tag{17b}$$

where $V_{g,i} = 2\alpha_i^2 p_i q_i$ is the contribution of the ith locus to the genic variance, $V_{i,\max}$ is the maximum possible value of $V_{g,i}$ (at allele frequencies one half), and the

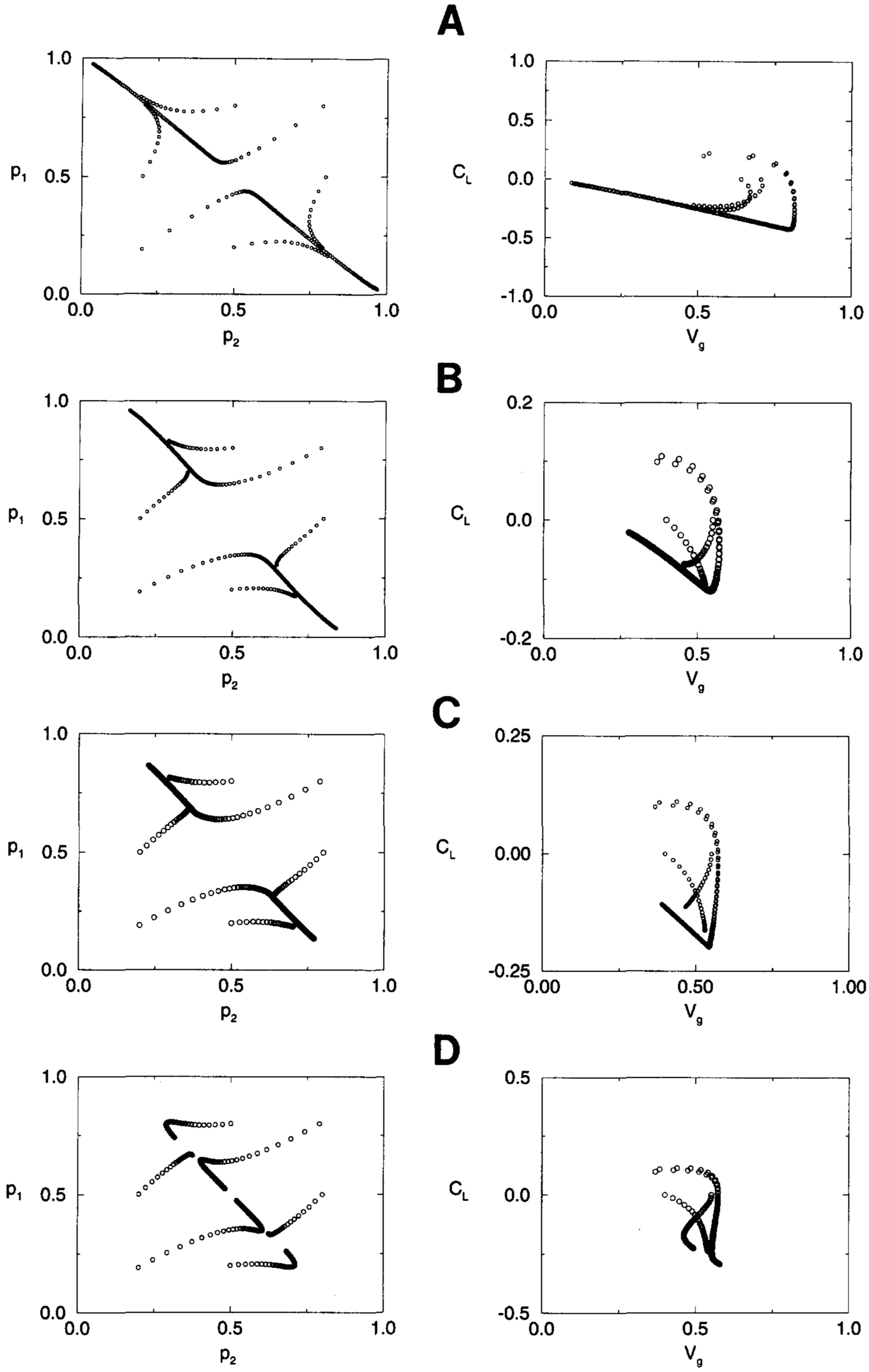

FIGURE 5.—Exact trajectories of (2) on the planes (p_1, p_2) and (V_g, C_L) under quadratic stabilizing selection with $s = 0.2$ and unequal contributions of the loci. (A) $r = 0.1$, $\alpha_2 = 0.8$, so that the system evolves to a monomorphic equilibrium. (B) $r = 0.1$, $\alpha_2 = 0.4$, so that the system evolves to a singly polymorphic equilibrium. (C) $r = 0.05$, $\alpha_2 = 0.4$, so that the system evolves to an "unsymmetic" doubly polymorphic equilibrium. (D) $r = 0.025$, $\alpha_2 = 0.4$, so that the system evolves to the "symmetric" doubly polymorphic equilibrium with allele frequencies one half.

constant depends on k and α_2. One can also derive an equation that describes the dynamics of $V_{g,i}$ and C_L on the phase-plane $(V_{g,i}, C_L)$. This equation is a special case of the Appel equation. Instead of trying to analyze it we present results of numerical iterations of the full system (2) in the form of projections on the phenotypic space (p_1, p_2) and (V_g, C_L). The system has four possible regimes (GAVRILETS and HASTINGS 1993) that correspond to evolution toward: (a) one of two monomorphic equilibria, (b) one of two singly polymorphic equilibria, (c) one of two "unsymmetric" doubly polymorphic equilibria, and (d) a "symmetric" polymorphic equilibrium with allele frequencies one half. As expected, in each of these cases on the (p_1, p_2) plane we observe (see Figure 5) a quick movement towards a straight line with slow evolution afterwards. The dynamics on the (V_g, C_L) plane are similar: a quick movement towards a straight line with slow evolution afterwards. The coordinates of these straight lines depend on the parameters of the model; increasing linkage decreases the rate of evolution.

EXAMPLE

In this section we consider how the theory developed in this paper can be used for analyzing results of artificial stabilizing selection experiments. The model we considered was a two locus one, but it has been argued that a small number of loci can account for observable variability in some quantitative traits (*e.g.*, LANDE 1988; ORR and COYNE 1992). Numerous papers with results of artificial stabilizing selection experiments have been published (*e.g.*, FALCONER 1957; PROUT 1962; GIBSON and THODAY 1963; SCHARLOO 1964; SCHARLOO *et al.* 1967; GIBSON and BRADLEY 1974; KAUFMAN *et al.* 1977; SOLIMAN 1982). In all these experiments the selection procedure used was double truncation: a small part q (usually between $\frac{1}{3}$ and $\frac{1}{5}$) of individuals with the phenotypes closest to the mean were selected. How is this translated into parameters of our model? Let the phenotype of an individual, z, be the sum of the genotypic value, g, and a random normally distributed microenvironmental deviation e having the zero mean and constant variance E. In APPENDIX C we show that the mean fitness of a genotype can be approximated as

$$w(g) \propto \exp\left(-\frac{g^2}{2E}\right). \tag{18}$$

This approximation is very good provided selection is at least moderately strong (say, with $q < \frac{1}{2}$). Several points concerning this approximation should be mentioned. The first is that the resulting fitness function is Gaussian. The second is that it does not depend on the proportion selected q (as long as $q < \frac{1}{2}$) and does not make any assumption about the number of loci. The third point concerns the strength of selection. Gaussian fitness functions are used in quantitative genetic models to describe natural stabilizing selection. The resulting mean fitness of genotypes in these models is $w(g) = \exp(-g^2/2V)$, with $V = V_s + E$, where V_s is a parameter characterizing the strength of selection on phenotypes. It has been argued that natural selection is typically weak with $V_s \approx 20E$ (TURELLI 1984) so that $V \approx 21E$. Expression (18) shows that at least in the case of artificial stabilizing selection $V \approx E$. Note also that new data have indicated that natural selection can be as strong as artificial selection (ENDLER 1986).

If initially the heritability coefficient $h^2 \approx \frac{1}{2}$, $C_L \approx 0$, and $V_g \approx 1$ (*i.e.*, the maximum possible level), then we can take $E \approx 1$. In the model with equal contributions of the loci this gives $\beta = 1 - \exp(-\frac{1}{2}) \approx 0.39$, $\delta = 1 - \exp(-2) \approx 0.86$. Figure 6 shows how θ depends on the recombination rate r for these values of β and δ. We see that even for unlinked loci the linkage disequilibrium generated by selection significantly decreases the phenotypic variance. Table 4 shows the time that it takes to reduce the genic variance from 0.95 to 0.5 and from 0.99 to 0.5 for some specific r values computed using (16). We see that for unlinked loci the time to reduce the genic variance is very short. Finite population size and initial deviation of V_g from 1 will reduce it further. The difference between values in the two last columns of Table 4 can be interpreted as the time interval during which there are no visible changes in the phenotypic characteristics. One can see that a decrease in recombination rate increases this time. LEWONTIN (1964) discovered this effect in numerical simulations.

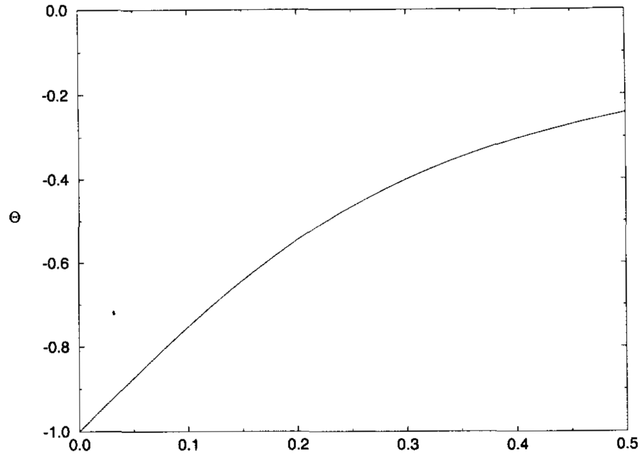

FIGURE 6.—The value θ as function of the recombination rate r for $\beta = 0.39$ and $\delta = 0.86$.

DISCUSSION

Two important points have traditionally been neglected in most theoretical studies of the evolution of multilocus systems. The first is the linkage disequilibrium that is expected to be generated by selection. The second is the transient behavior of different characteristics of populations such as genetic variability. In this paper we have gained insight into these questions using the simple but nevertheless important two locus model of stabilizing selection. The results we have obtained confirm our previous conclusion (GAVRILETS 1993; GAVRILETS and HASTINGS 1993, 1994a): linkage disequilibrium generated by selection can significantly affect qualitative and quantitative characteristics of populations provided selection is not extremely weak relative to recombination. This is true with respect to both the equilibrium and transient behavior. We have demonstrated how the interaction of selection and recombination results in constraints on the mode and rate of phenotypic evolution. Surprisingly, the transient dynamics in the model turns out to be quite simple. We have shown that evolution of the system on the (V_g, C_L) phase-plane occurs mainly along a straight line and used this property for predicting the rate of change of phenotypic characteristics of the population.

TABLE 4

Influence of the recombination rate on the dynamics

r	θ	$\mathscr{B}$	$\mathscr{D}$	$T_{V_g=0.95\rightarrow V_g=0.5}$	$T_{V_g=0.99\rightarrow V_g=0.5}$
0.50	–0.24	0.30	0.65	5	7
0.10	–0.75	0.10	0.21	23	35
0.01	–0.97	0.01	0.02	288	448

Our results demonstrate that if the loci are moderately linked, even strong stabilizing selection can require more than a hundred generations to change the genic variance significantly. This result has important implications for selection experiments and for the maintenance of genetic variability. Stabilizing selection experiments typically do not last more than tens of generations and employ strong selection. So our results imply that if dramatic reductions in variability occur, drift may in fact be more important than selection. When thinking about natural systems, it is unreasonable to expect that environmental conditions and populations remain constant over time scales of hundreds of generations. Our results imply that over shorter time scales, stabilizing selection will not have time to eliminate variability. Thus, the fact that at equilibrium variability cannot be maintained under stabilizing selection may be irrelevant–at time scales appropriate for some natural systems, variability is maintained.

A counter-intuitive conclusion of our analysis is that under conditions, which are plausible in artificial stabilizing selection experiments, the model can have a *stable* polymorphic equilibrium with *positive* linkage disequilibrium. This equilibrium is stable simultaneously with monomorphic equilibria. In this case the outcome of the evolution depends on the initial conditions. The approach we have developed allows us to use information about dynamics of observable characteristics of genetic systems under selection for testing hypotheses about properties of these systems. To have more practical value this approach should be generalized for the case of more than two loci and of finite population. Our preliminary numerical analyses have shown that some of the conclusions of this paper are valid in these more complex situations.

The main effects described in this paper are related to earlier conclusions of LEWONTIN (1964), BULMER (1971, 1974, 1980) and CHEVALET (1988). LEWONTIN (1964) numerically simulated stabilizing selection on an additive quantitative trait determined by 5 loci. He found that at first there is a rapid change both in allele frequencies (that brings the mean phenotype close to the optimum) and in linkage disequilibria. After this, allele frequencies and linkage disequilibria change slowly and this rate of change reduces with increases in linkage (reductions in recombination). We have shown how these changes are related to each other and to the parameters of the model by providing an analytical treatment of aspects of a two-locus model. BULMER (1971, 1974) considered a model in which selection does not change allele frequencies (due to an assumption about an effectively infinite number of loci with very small effects). He found an equation that described the dynamics of the linkage disequilibrium component if the loci are unlinked, and proposed an approximation that allowed computation of the equilibrium value of this component in the case of linked loci. Our analyses of dynamics have included both the case of linked loci and the case (obviously, more realistic) when allele frequencies change. Assuming multivariate normality of allele effects and no linkage, CHEVALET (1988) generalized Bulmer's approach in many directions. In particular, he took into account the change in allele frequencies under selection, demonstrated the separation of timescales, and analyzed the rate of evolution. Our analysis and conclusions are similar but are based on an exact multilocus genetic model and directly incorporate effects of linkage.

The results described in this paper are also relevant to more abstract questions. Our finding about constancy of the ratio C_l/V_g on the trajectories of the system seems to be related to the concept of "quasi-linkage equilibrium" introduced by KIMURA (1965). In Kimura's numerical simulations a specific function of gamete frequencies (namely, $Z = x_1x_4/x_2x_3$) was nearly constant even when all gamete frequencies were changing. NAGYLAKI (1976) has shown analytically that this is true but only if selection is very weak. Our results and a recent work by CHEVALET (1994) suggest that a function of gamete frequencies might be found that will behave as a "constant of motion" in more general situations. Also of some general interest may be the fact that in some sense the mode and the rate of the evolution in the model considered are determined by an unstable equilibrium.

We are grateful to CHUCK COXWELL who made numerical simulations that inspired this work. We thank SALLY OTTO for helpful comments on the manuscript. This work was supported by U.S. Public Health Service Grant R01 GM 32130 to A.H.

LITERATURE CITED

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

BODMER, W. F., and J. FELSENSTEIN, 1967 Linkage and selection: theoretical analysis of the deterministic two locus random mating model. Genetics **57:** 237–265.

BULMER, M., 1971 The effects of selection on genetic variability. Am. Nat. **105:** 210–211.

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

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

BÜRGER, R., 1986 Constraints for the evolution of functionally coupled characters: a nonlinear analysis of a phenotypic model. Evolution **40:** 182–193.

BÜRGER, R., 1993 Predictions for the dynamics of a polygenic character under directional selection. J. Theor. Biol. **162:** 487–513.

BÜRGER, R., and M. LYNCH, 1994 Evolution and extinction in a changing environment: a quantitative-genetic analyses. Evolution (in press).

Chevalet, C., 1988 Control of genetic drift in selected populations, pp. 379–394 in *Proceedings of the Second International Conference on Quantitative Genetics*, edited by B. S. Weir, E. J. Eisen, M. M. Godman, and G. Namkong. Sinaur Assoc., Sunderland, Mass.

Chevalet, C., 1994 An approximate theory of selection assuming a finite number of quantitative trait loci. Genet. Sel. Evol. (in press)

Coddington, E. A., and N. Levinson, 1955 *Theory of Ordinary Differential Equations.* McGraw-Hill, New York.

Endler, J. A., 1986 *Natural Selection in the Wild.* Princeton University Press, Princeton, N.J.

Falconer, D. S., 1957 Selection for phenotypic intermediates in Drosophila. J. Genet. **55:** 551–561.

Feldman, M. W., and U. Liberman, 1979 On the number of stable equilibria and the simultaneous stability of fixation and polymorphism in two-locus models. Genetics **92:** 1355–1360.

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

Gavrilets, S., and A. Hastings, 1993 Maintenance of genetic variability under strong stabilizing selection: a two locus model. Genetics **134:** 377–386.

Gavrilets, S., and A. Hastings, 1994a Maintenance of multilocus variability under strong stabilizing selection. J. Math. Biol. **32:** 287–302.

Gavrilets, S., and A. Hastings, 1994b A quantitative genetic model for selection on developmental noise. Evolution (in press).

Gibson, J. B., and Thoday, 1963 Effects of disruptive selection. VIII. Imposed quasi-random mating. Heredity **18:** 513–524.

Gibson, J. B., and B. P. Bradley, 1974 Stabilizing selection in constant and fluctuating environments. Heredity **33:** 293–302.

Hastings, A., 1987 Monotonic change of the mean phenotype in two-locus models. Genetics **117:** 583–585.

Hastings, A., 1989 Deterministic multilocus population genetics: an overview. Lect. Math. Life Sci. **20:** 27–54.

Hastings, A., and C. Hom, 1990 Multiple equilibria and maintenance of additive genetic variance in a model of pleiotropy. Evolution **44:** 1153–1163.

Hill, W. G., and A. Caballero, 1992 Artificial selection experiments. Annu. Rev. Ecol. Syst. **23:** 287–310.

Hoppenstead, F. C., 1976 A slow selection analysis of two locus, two allele traits. Theor. Popul. Biol. **9:** 68–81.

Karlin, S., and M. Feldman, 1970 Linkage and selection: two-locus symmetric viability model. Theor. Popul. Biol. **1:** 39–71.

Kaufman, P. F., F. D. Enfield and R. E. Comstock, 1977 Stabilizing selection for pupa weight in *Tribolium castaneum.* Genetics **87:** 327–341.

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

Kirkpatrick, M., and R. Lande, 1989 The evolution of maternal characters. Evolution **43:** 485–503.

Lande, R., 1979 Quantitative genetic analysis of multivariate evolution, applied to brain:body size allometry. Evolution **33:** 402–416.

Lande, R., 1988 Quantitative genetics and evolutionary theory, pp. 83–94 in *Proceedings of the Second International Conference on Quantitative Genetics*, edited by B. S. Weir, E. J. Eisen, M. M. Godman, and G. Namkong. Sinauer Assoc., Sunderland, Mass.

Lande, R., 1991 Isolation by distance in a quantitative trait. Genetics **128:** 443–452.

Lewontin, R. C., 1964 The interaction of selection and linkage. II. Optimal model. Genetics **50:** 757–782.

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

Nagylaki, T., 1977 The evolution of one- and two-locus systems. II. Genetics **85:** 347–354.

Nagylaki, T., 1978 *Selection in One- and Two-Locus Systems.* Springer, Berlin.

Nagylaki, T., 1992 *Introduction to Theoretical Population Biology.* Springer-Verlag, New York.

Nagylaki, T., 1993 The evolution of multilocus systems under weak selection. Genetics **134:** 627–647.

Orr, H. A., and J. A. Coyne, 1992 The genetics of adaptation–a reassessment. Am. Nat. **140:** 725–742.

Prout, T., 1962 The effect of stabilizing selection on the time of development in *Drosophila melanogaster.* Genet. Res. **3:** 364–382.

Scharloo, W., 1964 The effect of disruptive and stabilizing selection on the expression of a cubitus interruptus mutant in drosophila. Genetics **50:** 553–562.

Scharloo, W., M. S. Hoogmoed and A. Ter Kuile, 1967 Stabilizing and disruptive selection on a mutant character in drosophila. I. The phenotypic variance and its components. Genetics **56:** 709–726.

Soliman, M. H., 1982 Directional and stabilizing selection for developmental time and correlated response in reproductive fitness in *Tribolium castaneum.* Theor. Appl. Genet. **63:** 111–116.

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

Turelli, M., 1988 Phenotypic evolution, constant covariances, and the maintenance of additive variance. Evolution **42:** 1342–1347.

Turelli, M., and N. Barton, 1990 Dynamics of polygenic characters under selection. Theor. Popul. Biol. **38:** 1–57.

Uspensky, J. V., 1948 *Theory of Equations.* McGraw-Hill, New York.

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

Wolfram, S., 1988 *Mathematica: A System for Doing Mathematics by Computer.* Addison-Wesley, Reading, Mass.

Communicating editor: W. J. Ewens

APPENDIX A

Exact dynamic equations: If a double heterozygote has the optimum phenotype, *i.e.*, $z_0 = 0$, and the fitness function is symmetric, *i.e.*, $w(z - z_0) = w(z_0 - z)$, the two-locus model of stabilizing selection on an additive trait reduces to the symmetric viability model analyzed in a number of papers (see Bodmer and Felsenstein 1967; Karlin and Feldman 1970). Table 3 gives the fitnesses of different genotypes in this model. Here $\alpha = 1 - w(1 - \alpha_2)$, $\beta = 1 - w(1)$, $\gamma = 1 - w(\alpha_2)$, $\delta = 1 - w(1 + \alpha_2)$. We shall use the linear transformation (5). Note that $-1 \leq u, v, t \leq 1$ and that the new variables satisfy

$$u^2 \leq \frac{(1+t)^2}{4}, \qquad v^2 \leq \frac{(1-t)^2}{4}. \tag{A1}$$

We shall use these inequalities repeatedly. Using variables u, v, t, the dynamics of the system are (Karlin and Feldman 1970):

$$u' = \frac{1}{\bar{w}}[A_{11}(t)u + A_{12}(t)v], \tag{A2a}$$

$$v' = \frac{1}{\bar{w}}[A_{21}(t)u + A_{22}(t)v], \tag{A2b}$$

$$t' = \frac{1}{\bar{w}}\left[t - \frac{\delta}{8}((1+t)^2 + 4u^2) + \frac{\alpha}{8}((1-t)^2 + 4v^2) - r(t + v^2 - u^2)\right], \tag{A2c}$$

where

$$\bar{w} = 1 - \frac{\delta}{8}((1+t)^2 + 4u^2) - \frac{\alpha}{8}((1-t)^2 + 4v^2) - \frac{\beta}{4}(1 - t^2 + 4uv) - \frac{\gamma}{4}(1 - t^2 - 4uv), \tag{A2d}$$

and

$$A_{11}(t) = 1 - \frac{\delta}{2}(1 + t) - \frac{(\beta + \gamma)(1 - t)}{4},$$
$$A_{12}(t) = \frac{(\gamma - \beta)(1 + t)}{4}, \tag{A2e}$$

$$A_{22}(t) = 1 - \frac{\alpha}{2}(1 - t) - \frac{(\beta + \gamma)(1 + t)}{4},$$
$$A_{21}(t) = \frac{(\gamma - \beta)(1 - t)}{4} \tag{A2f}$$

One can use equations (A2) together with (6) to get dynamic equations in terms of the phenotypic characteristics $\bar{z}$, V_g and C_L.

Equal contributions of the loci: If the contributions of the loci are equal, then $\alpha = 0$, $\beta = \gamma$, and the dynamics of the system simplify to

$$u' = \frac{A_u(t)}{\bar{w}}u, \tag{A3a}$$

$$v' = \frac{A_v(t)}{\bar{w}}v, \tag{A3b}$$

$$t' = \frac{1}{\bar{w}}\left[t - \frac{\delta}{8}((1 + t)^2 + 4u^2) - r\,(t + v^2 - u^2)\right], \tag{A3c}$$

where

$$\bar{w} = 1 - \frac{\delta}{8}((1 + t)^2 + 4u^2) - \frac{\beta}{2}(1 - t^2), \tag{A3d}$$

and

$$A_u(t) = 1 - \frac{\delta}{2}(1 + t) - \frac{\beta}{2}(1 - t), \tag{A3e}$$

$$A_u(t) = 1 - \frac{\beta}{2}(1 + t). \tag{A3f}$$

HASTINGS (1987) showed that $0 < A_u(t) < \bar{w}$. That means that u monotonically approaches zero and, hence, at equilibrium $u = 0$. The consideration of the difference $A_v - \bar{w}$ with $u = 0$ shows that

$$A_v - \bar{w} = \frac{1 + t}{2}\beta\left(t - \frac{\delta}{4\beta}(1 + t)\right). \tag{A4}$$

One can see that if $\delta \geq 2\beta$, then $A_v \geq \bar{w}$ for all $-1 \leq t \leq 1$. Together with the fact that $A_v > 0$ that means that if $\delta \geq 2\beta$, then $|v'| > |v|$, and, hence, $v \to \mp 1$. At an equilibrium with $|v| = 1$, $t = -1$. Obviously, these equilibria correspond to fixation of gamete Ab or aB. If $\delta < 2\beta$, then there exists $t^* = \delta/(4\beta - \delta) > 0$ such that $|v'| > |v|$, if $t < t^*$, and $|v'| < |v|$, if $t > t^*$. The former case corresponds to the convergence of the population to one of two monomorphic equilibria. The latter case corresponds to a polymorphic equilibrium with $v = 0$ that exists and is stable provided t stays in the area where $t > t^*$. The consideration of the cubic equation for equilibrium values of t (with $u = v = 0$)

$$f(t) \equiv \frac{1 - t^2}{2}\beta\left(t - \frac{\delta}{4\beta}(1 + t)\right) - rt = 0 \tag{A5}$$

shows that if $\delta < 2\beta$, then there exists $r_c > 0$ such that for $0 < r < r_c$ this cubic has two solutions, say t_1 and t_2 ($t_1 < t_2$) between t^* and 1, and has no solutions if $\delta > 2\beta$. Note that if $r = 0$, than $t_1 = t^*$. The consideration of the equation for $t' - t$ shows that t_1 is unstable, while t_2 is stable. The critical value r_c can be found as follows. At $r = r_c$ the algebraic equations $f(t) = 0$ and $g(t) \equiv df(t)/dt = 0$ have a common root. This is possible if the resultant $R(f, g)$ of the polynomials f and g is zero (USPENSKY 1948). Hence, to find r_c we need to solve the algebraic equation $R(f, g) = 0$, which is cubic in our case. Result 1 in the main body of this report summarizes our findings.

We have already proved that u approaches zero while $|v|$ tends to one or zero depending on the parameter values and the initial conditions. Now we are going to show that u reaches its equilibrium value much quicker than v. Equations A3a and A3b can be represented as $u' = \lambda_u u$, $v' = \lambda_u v$ where $\lambda_i = A_i/\bar{w} > 0$. The closer λ_i is to unity, the slower the corresponding variables evolves. If both $A_u(t), A_v(t) < \bar{w}$, *i.e.*, if the system evolves to a polymorphic equilibrium with $u = v = 0$, $t = t_2$, then Equations A3e and A3f show that $A_u(t) < A_v(t)$. Hence, $\lambda_u < \lambda_v$, $u/v \to 0$, and u reaches zero much quicker then v. If $A_v(t) > \bar{w}$, *i.e.*, if the system evolves to a monomorphic equilibrium with $u = 0$, $|v| = 1$, $t = -1$, then using the first of the inequalities in (A1) one can show that

$$\bar{w} - A_u(t) \geq \frac{1 - t}{4}(\delta + t(\delta - 2\beta)) \tag{A6a}$$

and

$$A_v(t) - \bar{w} \leq \frac{1 + t}{4}(\delta + t(\delta - 2\beta)). \tag{A6b}$$

As the system evolves, $|v|$ increases, and not later than when $|v| = 1/2$, the t value becomes negative (see A1). Inequalities (A6) show that for negative t, λ_u lies farther from unity than λ_v, and, hence again u reaches its equilibrium value much quicker then v. Note that (A6) together with (A1) can be used to show that $|u' - u| > |v' - v|$ for all t values. Thus, we have shown that u reaches its equilibrium value much faster than v.

Non-equal contributions of the loci: In this subsection we consider the model of quadratic stabilizing selection with unequal contributions of the loci. We are going to show that in this case the dynamics on the (u, v) phase-plane are characterized by quick movement to a straight line along which the dynamics are slower. The dynamics on the (u, v) phase-plane are described by

$$\begin{pmatrix} u \\ v \end{pmatrix}' = \frac{1}{\bar{w}}A(t)\begin{pmatrix} u \\ v \end{pmatrix}, \tag{A7}$$

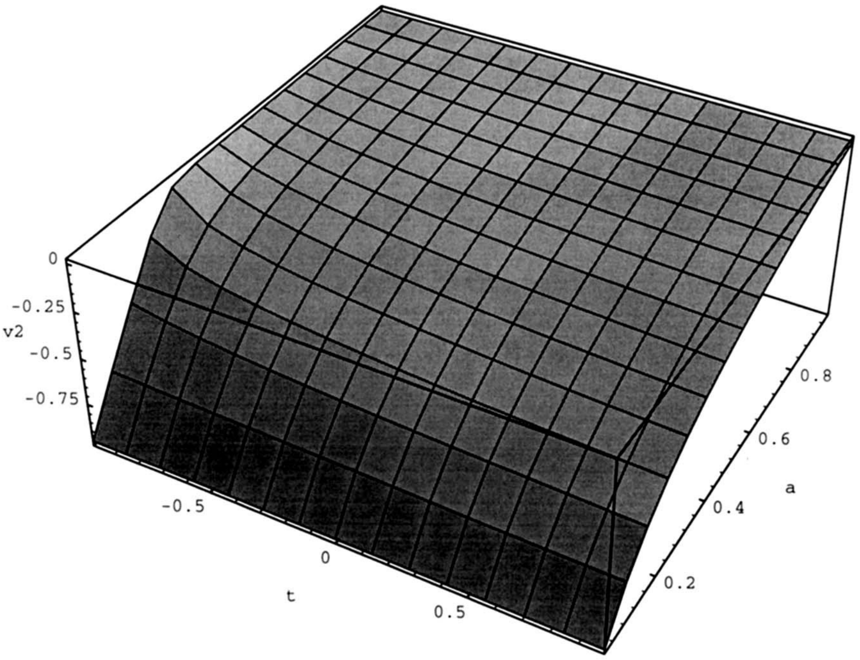

FIGURE 7.—The first component of vector vec_2 as function of t and α_2.

where the (2×2)-matrix $A(t)$ with elements $A_{ij}(t)$ is defined by (A2e–A2f). The eigenvalues of this matrix are:

$$\lambda_1 = 1 - \frac{s}{4}(3 + 3\alpha_2^2 + 4\alpha_2 t + \sqrt{Q}), \tag{A8a}$$

$$\lambda_2 = 1 - \frac{s}{4}(3 + 3\alpha_2^2 + 4\alpha_2 t - \sqrt{Q}), \tag{A*b}$$

with $\lambda_2 > \lambda_1$, while the corresponding eigenvectors are

$$\text{vec}_1 = \left\{\frac{(1 - \alpha_2^2)(1 + t)}{-4\alpha_2 - t - \alpha_2^2 t + \sqrt{Q}},\ 1\right\}, \tag{A9a}$$

$$\text{vec}_2 = \left\{\frac{(1 - \alpha_2^2)(1 + t)}{-4\alpha_2 - t - \alpha_2^2 t - \sqrt{Q}},\ 1\right\}, \tag{A9b}$$

where $Q = 1 + 14\alpha_2^2 + \alpha_2^4 + 8\alpha_2 t + 8\alpha_2^3 t + 4\alpha_2^2 t^2$. Figure 7 shows that the eigenvector vec_2 that corresponds to the biggest eigenvalue practically does not depend on t, and hence is practically constant during the evolution. Let us introduce the new variables (x, y):

$$\begin{pmatrix} u \\ v \end{pmatrix} = U\begin{pmatrix} x \\ y \end{pmatrix}, \tag{A10}$$

where matrix U is constructed from the column vectors (0, 1) and vec_2. The dynamics of (x, y) are described by

$$\begin{pmatrix} x \\ y \end{pmatrix}' = \frac{1}{\bar{w}} U^{-1} A(t) U \begin{pmatrix} x \\ y \end{pmatrix}. \tag{A11}$$

Matrix $U^{-1}A(t)U$ is a lower triangular matrix with diagonal elements λ_1 and λ_2 and a positive non-diagonal element. Since $\lambda_2 > \lambda_1 > 0$ for all t, the first component of vector (x, y) quickly approaches zero. In terms of the original variables u and v this corresponds to quick movement of the system to the straight line represented by the second eigenvector.

APPENDIX B

Approximate dynamics of (9): Equation 9 can be rewritten as $dC_L/dV_g = P(C_L, V_g)/Q(C_L, V_g)$ with the obvious interpretation. Simple methods for analyzing the phase portraits of such equations are well known (*e.g.*, CODDINGTON and LEVINSON 1955). The phase-plane of (9) is restricted by (10). The nullclines of V_g are (i) $V_g = 1$ and (ii) $C_L = -V_g$; the only nullcline of C_L that belongs to the feasible part of the phase-plane is (iii) $C_L = r/s - \sqrt{(r/s)^2 + V_g^2}$ (the nullcline $C_L = r/s + \sqrt{(r/s)^2 + V_g^2}$ is not a part of the feasible area because on this nullcline $C_L > V_g$). Equation 9 has two equilibria at intersections of the nullclines: (0, 0) and $(1, \theta)$, where θ is given by (11). The equilibrium point (0, 0) is a stable node; the corresponding eigenvalues are equal to $-s$ and $-r$. This equilibrium of (9) corresponds to two monomorphic equilibria of (2) with fixation of gamete *Ab* or *aB*. The latter are identical in phenotypic terms. The equilibrium $(1, \theta)$ is a saddle; the corresponding eigenvalues are $\lambda_1 = s + r - \sqrt{s^2 + r^2} > 0$ with the eigenvector $(-1 - r/s, 1)$ and $\lambda_2 = -\sqrt{s^2 + r^2} < 0$ with the eigenvector (0, 1). This equilibrium of (9) corresponds to the unstable equilibrium of (2) with allele frequencies equal to one half and linkage disequilibrium $D = \theta/4$. The nullcline $V_g = 1$ is a stable manifold for the equilibrium $(1, \theta)$: the system evolves to this equilibrium if initially $V_g = 1$. In the neighborhood of an equilibrium the dynamics are determined by the corresponding eigenvalues and eigenvectors. Let us consider the ratio of the absolute values of the eigenvalues at $(1, \theta)$. One can easily see that $|\lambda_1|/|\lambda_2| = 2|\theta|(1 + \theta)/(1 + \theta^2)$. The latter value is always less then 0.42. That shows that at a neighborhood of $(1, \theta)$ the dynamics of

(9) are characterized by two different time scales with a quick movement towards the unstable manifold (represented locally by the eigenvector $(-1 - r/s, 1)$) and a slow movement along this manifold. We are going to show that the same description of the dynamics is valid not only at a neighborhood of $(1, \theta)$ but on the whole phase-space, *i.e.*, globally. Let us consider the value of dC_L/dV_g on the straight line that connects the equilibria $(0, 0)$ and $(1, \theta)$. Using the fact that θ satisfies the equation $r\theta + s(1 - \theta^2)/2 = 0$, one can show that $dC_L/dV_g|_{C_L = \theta V_g} = (\theta - 1)/2$ and, hence,

$$\left.\frac{dC_L}{dV_g}\right|_{C_L=\theta V_g} < \theta. \tag{B1}$$

This means that the trajectories of (9) intersect the line $C_L = \theta V_g$ from below. We can already see that all the trajectories of (9) enter a narrow area restricted by this line and the nullcline (iii) of C_L. We can narrow this area further. Let us consider the value of dC_L/dV_g on the straight line $C_L = \theta V_g + \epsilon$ that is parallel with $C_L = \theta V_g$ and lies a little higher then the latter. We are going to show that if ϵ is greater then some small number, then

$$\left.\frac{dC_L}{dV_g}\right|_{C_L=\theta V_g+\epsilon} > \theta. \tag{B2a}$$

This means that the trajectories of (9) intersect the line $C_L = \theta V_g + \epsilon$ from above. One can show that the latter inequality is equivalent to

$$-\epsilon^2\theta - (1 + \theta^2)\epsilon - \theta(1 + \theta)^2 V_g(1 - V_g) < 0. \tag{B2b}$$

In particular (B2b) is always satisfied for $\epsilon \geq 0.035$. Inequalities (B1-B2a) mean that trajectories of (9) enter a narrow area between lines $C_L = \theta V_g$ and $C_L = \theta V_g + \epsilon(V_g, \theta)$, where $\epsilon(V_g, \theta) < 0.035$. Numerical iterations show that all the trajectories of (9) approach the line $C_L = \theta V_g$ very closely (see Figure 1).

Approximate dynamics of (14): Let us assume that the polymorphic equilibrium $(1, C_L^*)$ exists. One can easily see that the trajectories of (14) intersect the line $C_L = 4\beta/(3\beta - (\delta - \beta)) - V_g$ from above. This line is one of the three nullclines of V_g; on it the term in the squared brackets in (14) is zero. Thus, if initially $C_L \leq 4\beta/(3\beta - (\delta - \beta)) - V_g$, then the system cannot evolve towards this state. This shows that the domain of attraction of the polymorphic state is small (see Figure 3).

Now let us assume that the system evolves toward one of the two monomorphic equilibria (with gamete *Ab* or *aB* fixed). In phenotypic terms these equilibria are equivalent and are represented by the point $(0, 0)$ on the phase-plane (V_g, C_L). This point describes the stable equilibrium of (14). Besides, (14) has an (unstable) equilibrium $(1, \theta)$, where $\theta < 0$, at the intersection of the nullcline $V_g = 1$ of V_g with the nullcline of C_L that is defined by the numerator of the right-hand part of (14). The equilibrium $(1, \theta)$ is approached only if $V_g = 1$ initially. The third nullcline of V_g is given by $V_g + C_L = 0$. Let us consider the direction of the trajectories of (14) on the line that connects $(0, 0)$ with $(1, \theta)$. If $\delta > 2\beta$, then inequality (B1) is still valid. If $\delta \leq 2\beta$, then the derivative dC_L/dV_g can change sign on the straight line $C_L = \theta V_g$. However, one can still show that the trajectories of (14) enter a narrow area R restricted by two straight lines parallel with $C_L = \theta V_g$ one of which lies higher and another lower then $C_L = \theta V_g$. Let us consider the difference

$$\left.\frac{dC_L}{dV_g}\right|_{C_L=\theta V_g+\epsilon} - \theta. \tag{B3}$$

Putting the terms in this difference over a common denominator (which is positive), one can see that the numerator can be represented as $\mathrm{Num} = f_1(\theta, x, \epsilon) + df_2(\theta, x, \epsilon)$, where $d = (\delta/4\beta) - 1 \geq -3/4$ and f_i are polynomials in θ, x and ϵ. The consideration of the graph of $f_2(\theta, x, \epsilon)$ using *Mathematica* software (WOLFRAM 1988) shows that $f_2 < 0$ at $\epsilon = -0.03$ for all feasible θ and x. That means that Num reaches its maximum at $d = -3/4$. The consideration of the graph of Num at $d = -3/4$ and $\epsilon = -0.03$ shows that it is negative for all feasible θ and x. Altogether this means that the trajectories of (14) intersect the line $C_L = \theta V_g - 0.03$ from below. In a similar way the consideration of the graph of $f_2(\theta, x, \epsilon)$ shows that $f_2 > 0$ at $\epsilon = 0.10$. That means that Num reaches its minimum at $d = -3/4$. The consideration of the graph of Num at $d = -3/4$ and $\epsilon = 0.10$ shows that it is positive for all feasible θ and x. Altogether this means that the trajectories of (14) intersect the line $C_L = \theta V_g + 0.10$ from above. Thus, we have shown that all the trajectories of (14) enter a narrow area restricted by two straight $C_L = \theta V_g - 0.03$ and $C_L = \theta V_g + 0.10$. Numerical iterations show that all the trajectories of (14) approach the line $C_L = \theta V_g$ very closely.

APPENDIX C

The mean fitness of genotype under double truncation: Let the phenotype of an individual, z, be the sum of the genotypic value, g, and a random normally distributed microenvironmental deviation e having mean zero and constant variance E. Let the mean value of the trait be zero, and select for the next generation the individuals with $-z_q < z < z_q$, where z_q is the truncation point that corresponds to the proportion q selected. In this case the mean fitness of an individual with genotypic value g is $w(g) = \Phi((z_q - g)/\sqrt{E}) - \Phi((-z_q - g)/\sqrt{E})$, where $\Phi(x)$ is the distribution function of a standard normal variable. In a vicinity of 0 (say for $1/4 < \Phi(x) < 3/4$), $\Phi(x)$ is excellently approximated by a linear function. This, together with the assumption that the phenotypic distribution is normal, allows us to approximate z_q as $q\sqrt{\pi/2P}$, where P is the phenotypic variance. Now $z_q/\sqrt{E} = q\sqrt{\pi/2(1 - h)^2}$, where $h^2 = G/P$ is the heritability. Assuming that $z_q/\sqrt{E} < 1$ (which is true, for example, for $q < 1/2$ and $h^2 < 1/2$) and expanding $\Phi((z_q - g)/\sqrt{E})$ and $\Phi((-z_q - g)/\sqrt{E})$ in Taylor series at the point $-g/\sqrt{E}$, we finally find that the mean fitness of genotype can be approximated as (18). The error of this approximation is $O((z_q/\sqrt{E})^3)$.