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The divergence of a polygenic system subject to stabilizing selection, mutation and drift

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Summary

Polygenic variation can be maintained by a balance between mutation and stabilizing selection. When the alleles responsible for variation are rare, many classes of equilibria may be stable. The rate at which drift causes shifts between equilibria is investigated by integrating the gene frequency distribution $\bar{W}^{2N}\prod(pq)^{4N\mu-1}$. This integral can be found exactly, by numerical integration, or can be approximated by assuming that the full distribution of allele frequencies is approximately Gaussian. These methods are checked against simulations. Over a wide range of population sizes, drift will keep the population near an equilibrium which minimizes the genetic variance and the deviation from the selective optimum. Shifts between equilibria in this class occur at an appreciable rate if the product of population size and selection on each locus is small ($Ns\alpha^2 < 10$). The Gaussian approximation is accurate even when the underlying distribution is strongly skewed. Reproductive isolation evolves as populations shift to new combinations of alleles: however, this process is slow, approaching the neutral rate ($\approx\mu$) in small populations.

1. Introduction

How is polygenic variation maintained, and how does it evolve? How does a population separate into two incompatible species? How can a population search through the vast space of possibilities to find better adapted combinations of alleles? How is selection on the whole organism reflected in the evolution of individual genes? Because many genes interact to produce the observable phenotype, these questions have proved hard to approach, either empirically or theoretically.

In this paper, I will analyse the effects of sampling drift on polygenic variation which is maintained by a balance between mutation and stabilizing selection. A character is determined by the sum of effects of a large number of genes, each of which segregates for two alleles. Stabilizing selection tends to reduce variation, and is strong enough that each gene is close to fixation. This model was first proposed by Wright (1935); it has since been elaborated by Latter (1960), Bulmer (1972, 1980), Kimura (1981), Barton (1986), Hastings (1987), and Burger *et al.* (1988). Despite its simplicity, it is relevant to each of the issues raised above.

Since most quantitative characters must be subject to stabilizing selection, at least in the long run, some other force must maintain variability. The simplest possibility is that mutation alone is responsible for the high heritabilities which are found in nature (Lande, 1975). If this is so, one might hope that the genetic variance could be predicted from measurable quantities, such as the total mutation rate, the effective number of loci, and the strength of selection. Unfortunately, predictions depend on the distribution of allelic effects at individual loci: if a large number of alleles segregate, giving an approximately Gaussian distribution, then the variance is proportional to the square root of the ratio between mutation rate and selection pressure, whereas if variation depends on rare alleles with large effects, it is directly proportional to this ratio (Turelli, 1984). In general, the evolution of the mean and variance of a character (which are usually all that can be measured) depends on the higher moments of the underlying distribution of allelic effects: only by making strong and unrealistic assumptions can a closed set of equations be obtained (Barton & Turelli, 1987). Even when all the loci are close to fixation, as in the case considered here, the outcome may still be unpredictable. Barton (1986) showed that many stable equilibria can coexist: the genetic variance can range from that given by the 'rare allele' approximation up to that given by the Gaussian approximation. So, the phenotypic state depends on how populations move between different equilibria.

Since many different combinations of alleles may be able to satisfy the constraints imposed by selection, many distinct stable equilibria will generally be available. Wright (1932; Provine, 1986) illustrated this point using the 'adaptive landscape': a graph of mean fitness plotted against the possible states of the population. In all but the simplest cases, this surface will contain many local 'adaptive peaks'. The central problem for Wright was how populations can move towards superior peaks, despite their tendency to be trapped by local irregularities in the surface. He proposed that sampling drift, or perhaps random fluctuations in selection pressures, could knock populations between peaks, and that, for a variety of reasons, populations would tend to accumulate at the higher peaks. Here, I consider just one factor which favours higher peaks: random transitions from low peaks to high tend to be more likely than those in the opposite direction. In the present model of a quantitative character, the question is whether this tendency is efficient enough that the population will usually be in the equilibrium with lowest variance, and the highest mean fitness. If this is so, then the simple 'rare alleles' approximation can safely be used to predict the evolution of the mean and variance.

Shifts between alternative equilibria are important even if they have no direct phenotypic or adaptive consequences. Even when stabilizing selection is strong enough that the phenotype is confined within narrow limits, shifts between different combinations of alleles may still be possible. This process is of interest from two points of view. First, the rate and pattern of substitution at individual loci will be affected by selection (Kimura, 1981, Hastings, 1987, Foley, 1987): is the observed level of selection on the whole organism consistent with effectively neutral evolution at the molecular level? Second, two populations may eventually come to have very different combinations of alleles, leading to substantial reproductive barriers between them. How rapid is this process, relative to other mechanisms of speciation?

Progress on these questions depends on techniques for analysing stochastic systems with many degrees of freedom. Though such techniques are well developed in other fields, their application to genetical problems requires some innovations. The simple model analysed here is interesting in its own right. However, the main aim is to develop methods which can deal with evolution in many dimensions.

2. Deterministic behaviour

The deterministic behaviour of the model is described by Barton (1986); this section summarizes the necessary results. Consider a single character, z, which is determined by the sum of effects of n biallelic loci. Individuals are diploid. Substitutions at all loci have an identical effect α on the character; its value must therefore range between $-n\alpha$ and $+n\alpha$. The character is assumed to be completely heritable: environmental variation would merely weaken selection, and would have no qualitative effect. Individual fitness follows a Gaussian curve centred on some optimum z_0, and with variance $1/s$.

Provided that selection is weak, the population can be considered to change approximately continuously in time. If selection is also much slower than recombination, linkage disequilibrium can be neglected (Bulmer, 1980; see Turelli & Barton, 1989, for a general justification). The effects of selection are then given by the general relation:

$$\frac{dp_i}{dt} = \frac{p_i q_i}{2} \frac{\partial \log(\bar{W})}{\partial p_i} \tag{1}$$

(p_i, q_i are the frequencies of the + and − alleles at the ith locus).

If the number of loci is large, and selection is weak, then the mean fitness, $\bar{W}$, of a population with mean z and variance v is approximately:

$$\log(\bar{W}) = -\frac{s(z-z_0)^2}{2} - \frac{sv}{2} \tag{2}$$

where

$$z = \sum_i \alpha(p_i - q_i), \quad v = \sum_i 2\alpha^2 p_i q_i$$

Including mutation at an equal rate μ in each direction:

$$\frac{dp_i}{dt} = \frac{s\alpha^2}{2} p_i q_i [(p_i - q_i) - 2\delta] - \mu(p_i - q_i). \tag{3}$$

Here, $\delta = (z - z_0)/\alpha$ is the deviation from the optimum relative to the effect of a substitution at a single locus.

The equilibria of eqn (3) satisfy a cubic; provided that δ and μ are not too large ($|\delta| < \frac{1}{2}$, $\mu < s\alpha^2/8$; Barton, 1986), it has three solutions, denoted by $[p, \rho, P]$. The equilibria which can be reached by the whole system can be described by the numbers of loci which are at each of these three frequencies, $[m, \nu, M]$ ($m + \nu + M = n$). Each combination [m, ν, M] represents a class of equilibria with the same overall properties, but includes many different permutations across loci.

The deterministic equilibria can be calculated by solving eqn (3) numerically (Table 1). The nature of the stable equilibria depends on the ratio between mutation and selection at each locus. When this is extremely small ($\mu < s\alpha^2/(n+1)^2$), mutation is negligible: one locus can be kept polymorphic by (effectively) heterozygote advantage, whilst the remainder contribute negligible variance. At the other extreme, when $\mu > s\alpha^2/8$, selection is negligible, and all loci are kept polymorphic by recurrent mutation. In the intermediate range, $s\alpha^2/(n+1)^2 < \mu < s\alpha^2/8$, all loci are close to fixation for one or other allele (i.e., all stable equilibria are of the class $[m, 0, M]$). However, several different classes of stable equilibria may exist: approximately $1 + (n-2)\sqrt{\mu/s\alpha^2}$. Though the phenotypic means of these alternatives are never

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Table 1. *Properties of the deterministic equilibria*

m	ν	M	p	ρ	P	z	v	$\log(\bar{W})$	U	λ	$\log(D)$
(*a*) $n = 100$, $\gamma = 0{\cdot}01$, $z_0 = 0$, $s = 1$, $\alpha = 0{\cdot}1$											
45	0	55	0·0123		0·9018	0·0311	0·1084	−10·9367	−26·9722	−0·0087	−232·578
45	1	54	0·0123	0·8967	0·9018	0·0311	0·1084	−10·9367	−26·9722	0·0087	−230·567
46	0	54	0·0124		0·9181	0·0307	0·0924	−9·3371	−25·7974	−0·0760	−113·211
46	1	53	0·0124	0·8750	0·9189	0·0306	0·0924	−9·3345	−25·7979	0·0718	−110·784
47	0	53	0·0126		0·9349	0·0292	0·0762	−7·7107	−24·6551	−0·1670	−70·365
47	1	52	0·0127	0·8400	0·9366	0·0289	0·0761	−7·7003	−24·6602	0·1466	−67·237
48	0	52	0·0132		0·9517	0·0255	0·0603	−6·1039	−23·6034	−0·3033	−40·404
48	1	51	0·0135	0·7754	0·9548	0·0244	0·0602	−6·0826	−23·6305	0·2345	−36·050
49	0	51	0·0150		0·9675	0·0169	0·0465	−4·6798	−22·7701	−0·5351	−17·087
49	1	50	0·0163	0·6292	0·9725	0·0118	0·0470	−4·7224	−22·8978	0·3127	−11·850
50	0	50	0·0204		0·9795	0·0000	0·0400	−4·0000	−22·4207	−0·9200	−6·066
⋮					⋮			⋮		⋮	
55	0	45	0·0981		0·9876	−0·0311	0·1084	−10·9367	−26·9722	−0·0087	−232·578
(*b*) $n = 100$, $\gamma = 0{\cdot}01$, $z_0 = 5$, $s = 1$, $\alpha = 0{\cdot}1$											
17	0	83	0·0123		0·9029	5·0311	0·1496	−15·0580	−28·9093	−0·0130	−345·123
17	1	82	0·0123	0·8955	0·9030	5·0311	0·1496	−15·0579	−28·9093	0·0129	−343·073
18	0	82	0·0124		0·9137	5·0309	0·1336	−13·4551	−27·7326	−0·0563	−221·620
18	1	81	0·0124	0·8820	0·9141	5·0309	0·1335	−13·4532	−27·7328	0·0541	−219·291
19	0	81	0·0124		0·9248	5·0303	0·1172	−11·8182	−26·5705	−0·1088	−165·923
19	1	80	0·0125	0·8638	0·9256	5·0302	0·1172	−11·8115	−26·5719	0·1007	−163·181
20	0	80	0·0126		0·9361	5·0290	0·1006	−10·1507	−25·4413	−0·1750	−126·223
20	1	79	0·0127	0·8383	0·9373	5·0288	0·1005	−10·1341	−25·4469	0·1540	−122·831
21	0	79	0·0130		0·9475	5·0267	0·0839	−8·4617	−24·3754	−0·2633	−93·023
21	1	78	0·0131	0·7996	0·9494	5·0262	0·0835	−8·4263	−24·3929	0·2155	−88·524
22	0	78	0·0138		0·9590	5·0225	0·0672	−6·7755	−23·4274	−0·3910	−62·404
22	1	77	0·0141	0·7343	0·9618	5·0210	0·0666	−6·7052	−23·4790	0·2832	−55·824
23	0	77	0·0156		0·9702	5·0144	0·0514	−5·1701	−22·7037	−0·5960	−32·316
23	1	76	0·0170	0·6029	0·9743	5·0094	0·0504	−5·0521	−22·8635	0·3326	−21·706
24	0	76	0·0209		0·9801	4·9987	0·0394	−3·9473	−22·4223	−0·8920	−4·564
24	1	75	0·0310	0·3272	0·9846	4·9843	0·0414	−4·1741	−22·9494	0·2709	4·329
25	0	75	0·0382		0·9858	4·9789	0·0393	−3·9760	−22·8680	−0·4302	4·823
25	1	74	0·0654	0·1547	0·9873	4·9708	0·0516	−5·2547	−23·8739	0·1271	−11·661
26	0	74	0·0686		0·9874	4·9704	0·0516	−5·2516	−23·8702	−0·1452	−14·177
(*c*) $n = 100$, $\gamma = 0{\cdot}0025$, $z_0 = 0$, $s = 1$, $\alpha = 0{\cdot}2$											
48	0	52	0·0027		0·9627	0·0796	0·1596	−4·1502	−9·4002	−0·0580	−115·415
48	1	51	0·0027	0·9314	0·9634	0·0795	0·1596	−4·1486	−9·4006	−0·0552	−112·680
49	0	51	0·0029		0·9810	0·0704	0·0874	−2·3099	−7·8931	−0·2213	−48·232
49	1	50	0·0030	0·8486	0·9835	0·0670	0·0871	−2·2902	−7·9114	0·1698	−40·762
50	0	50	0·0050		0·9949	0·0000	0·0400	−1·0000	−6·9915	−0·9800	−0·908
⋮					⋮			⋮		⋮	
52	0	48	0·0372		0·9972	−0·0796	0·1596	−4·1502	−9·4002	−0·0580	−115·415
(*d*) $n = 25$, $\gamma = 0{\cdot}01$, $z_0 = 0$, $s = 1$, $\alpha = 0{\cdot}2$											
12	0	13	0·0137		0·9577	0·0463	0·0550	−1·4307	−5·8564	−0·3734	−6·732
12	1	12	0·0204	0·5000	0·9795	0·0000	0·0584	−1·4600	−5·9641	0·1107	−2·869
13	0	12	0·0422		0·9862	−0·0463	0·0550	−1·4307	−5·8564	−0·3734	−6·732

Notation: $[m, \nu, M]$, numbers of loci at the three possible equilibria; $[p, \rho, P]$, the corresponding allele frequencies; z, v, the mean and variance of the character; $\log(\bar{W})$, U, the log mean fitness, and the potential function which accounts for mutation; λ, the leading eigenvalue (negative for a stable equilibrium); $\log(D)$, the log of the absolute value of the determinant of the stability matrix (i.e. the log of the product of the eigenvalues). Where $z_0 = 0$ (*a*, *c*, *d*), the tables are symmetrical; here, only one set of equilibria are shown.

far from the optimum ($|\delta| < \frac{1}{2}$), the phenotypic variance may differ substantially. In this deterministic case, therefore, the amount of variation that can be maintained by a mutation/selection balance depends on the history of the population.

The stability of the equilibria is determined by the eigenvalues of the matrix $\partial(\mathrm{d}p_i/\mathrm{d}t)/\partial p_j$, which governs the dynamics near equilibrium. Whenever an equilibrium of the class $[m, 0, M]$ exists, it is stable: all the eigenvalues are negative. The degree of stability can be measured by the product of (minus) these eigenvalues ($D \equiv \det(-\partial(\mathrm{d}p_i/\mathrm{d}t)/\partial p_j)$); we will see in

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the next section that this quantity is important in the stochastic behaviour of the system. For the stable equilibria $[m, 0, M]$:

$$D = g^{m-1}G^{M-1}\det\begin{bmatrix}(g+4mpq) & 4MPQ\\ 4mpq & (G+4MPQ)\end{bmatrix} \quad (4a)$$

where $g = 1-6pq+4\mu/s\alpha^2-2\delta(p-q)$

$G = 1-6PQ+4\mu/s\alpha^2-2\delta(P-Q)$

(from eqn 12) in Barton, 1986; note the difference in sign in the definition of g, G here).

To move from one stable equilibrium to another, the population must pass through an unstable state. In general, the most likely path for such a transition is via an unstable equilibrium; the chances of such a transition depend on the dynamics near this equilibrium (Barton & Rouhani, 1987). Though I will not attempt a formal proof, it seems certain that the most likely route from an equilibrium of the class $[m, 0, M]$ to an adjacent equilibrium $[m+1, 0, M-1]$ is via the unstable state $[m, 1, M-1]$ (Fig. 5). This corresponds to a shift of one of the loci from near fixation for the + allele, through a polymorphism, to near fixation for the − allele, as this shift occurs, allele frequencies at all the other loci adjust so as to keep the mean close to the optimum.

Numerical results show that whenever an equilibrium of the class $[m, 1, M]$ exists, it is unstable: one eigenvalue is positive, whilst the remaining $(n-1)$ are negative. The degree of instability can still be measured by the product of (minus) the eigenvalues, which is now negative:

$$D = g^{m-1}G^{M-1}\det\begin{bmatrix}(g+4mpq) & 4pq & 4Mpq\\ 4m\rho\bar{\rho} & (\Gamma+4\rho\bar{\rho}) & 4M\rho\bar{\rho}\\ 4mPQ & 4PQ & (G+4MPQ)\end{bmatrix} \quad (4b)$$

(where Γ is defined in the same way as g, G above; $\bar{\rho} = \rho$).

Thus far, the deterministic behaviour has been described by a set of differential equations (3), coupled together by the deviation, δ. The stochastic analysis below rests on the fact that the dynamics of this model can also be described in terms of a potential function, U:

$$\frac{dp_i}{dt} = \frac{p_i q_i}{2}\frac{\partial U}{\partial p_j} \quad (5)$$

where

$$U \equiv \log(\bar{W}) + 2\mu\log(V), \quad V = \prod_{i=1}^{n}\left(\frac{p_i q_i}{2}\right).$$

The rate of change of allele frequency is given by the product of the additive genetic variance $(p_i q_i/2)$ and the gradient of U. The population can be seen as climbing towards local peaks of U, on a surface which represents the graph of U plotted against allele frequency. This surface is not quite the same as Wright's 'adaptive topography', because it includes the effects of mutation: peaks of U do not coincide with peaks in mean fitness, because mutation maintains maladaptive polymorphism. The stability of an equilibrium depends on the curvature of the potential surface $(\partial^2 U/\partial p_i \partial p_j)$ near a stationary point. This is related to the eigenvalues discussed above:

$$D = V\det(\partial^2 U/\partial p_i \partial p_j). \quad (6)$$

The deterministic properties of the system are summarised in Table 1, for various parameter combinations.

3. Stochastic behaviour: simple approximations

The three central questions are: first, what is the distribution of the phenotypic mean and variance? Second, what is the chance that a population will be in the vicinity of one deterministic equilibrium out of the many alternatives? Third, how often do populations shift between equilibria? A full answer to these questions must follow the whole set of allele frequencies. However, before beginning the multidimensional analysis, it will be helpful to discuss some simple approximations.

The distribution of the mean and variance

In the limit where the alleles responsible for polygenic variation are rare, and where the distribution of breeding values is symmetric, changes in the mean and variance under selection and mutation are approximated by:

$$\begin{matrix}\frac{dz}{dt}\\ \frac{dv}{dt}\end{matrix} = \begin{pmatrix}v & 0\\ 0 & v\alpha^2\end{pmatrix}\begin{pmatrix}-s(z-z_0)\\ -s/2\end{pmatrix} + \begin{pmatrix}0\\ 2n\mu\alpha^2\end{pmatrix} \quad (7a)$$

(from Barton, 1986, eqn 14, setting the third moment to zero).

The effects of drift are given by the same matrix that mediates the effects of selection in eqn (7*a*) (Barton & Turelli, 1987, eqn (3.7)). The covariance of random fluctuations in the mean and variance is:

$$\begin{pmatrix}E(\delta z^2) & E(\delta z\,\delta v)\\ E(\delta z\,\delta v) & E(\delta v^2)\end{pmatrix} = \frac{1}{N}\begin{pmatrix}v & 0\\ 0 & v\alpha^2\end{pmatrix} \quad (7b)$$

(where N is the effective number of diploid individuals).

Sampling drift will also decrease the expected variance by a factor $(1-1/2N)$ in each generation. The expectations of the mean and variance can be found by setting eqn (7*a*) to zero. The variance of the mean is given by $E(\delta z^2)/2\lambda$, where $\lambda = s$ is the rate of return to the equilibrium mean.

Similarly, the variance of the variance is $E(\delta v^2)/2\lambda$,

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where λ is now the rate of return to the equilibrium variance. The λ are derived from eqn (7*a*).

$$E(z) = z_0 \qquad \mathrm{var}(z) = \frac{1}{2Ns}$$

$$E(v) = \frac{4n\mu}{s(1+[1/Ns\alpha^2])} \quad \mathrm{var}(v) = \left(\frac{4n\mu}{Ns^2}\right)\frac{1}{(1+[1/Ns\alpha^2])^2}. \tag{8}$$

The formula for the expected genetic variance, $E(v)$, was obtained heuristically by Burger *et al.* (1988). Fluctuations in the mean, var(z), depend only on the product of population size and selection on the phenotype (Ns), and are independent of the genetic variance, v. This is because both the size of perturbations due to drift, and the response to selection, increase with v; these two effects cancel (Lande, 1975). The variance of the genetic variance also depends only on measurable, phenotypic parameters; the question addressed below is whether the genetics underlying these parameters significantly distort these phenotypic approximations.

Substitution rates

In the parameter range we are considering, a shift between equilibria approximates to a substitution at a single locus. As this substitution occurs, allele frequencies at all the other loci adjust to keep the mean near the optimum. The simplest case is where the population is sufficiently small, and selection at each locus sufficiently weak, that substitutions are effectively neutral ($Ns\alpha^2 \ll 1$). Then, the rate of substitution at each locus is just μ. This neutral approximation sets an upper limit to the substitution rate: for symmetric equilibria at least, stabilizing selection must reduce the rate.

Next, consider the dynamics of one locus in isolation. One might assume that adjustments at all the other loci keep the mean at the optimum, and calculate the rate of substitution from eqn (3) alone; this was the approach taken by Kimura (1981). However, there are two difficulties. First, the mean will generally deviate from the optimum, and this deviation will change during the substitution. Neglecting the deviation altogether (i.e. $\delta = 0$) gives a poor approximation, which does not distinguish between different classes of equilibria. One can instead interpolate between the deviations at the upper and lower equilibria (i.e. $\delta = \delta_+ p + \delta_- q$). This method is still approximate, since the deviation does not change linearly (see Table 1), and since the probability of a shift depends on the magnitude of transverse fluctuations, as well as on the dynamics along the main path.

A second difficulty is that when many mutations enter the population in each generation ($4N\mu > 1$), one cannot calculate the rate of change from the probability of fixation of individual mutations. This problem is treated by Barton & Rouhani (1987), who give a formula for the single locus case which is valid with recurrent mutation.

4. Stochastic behaviour: multidimensional analysis

Background

Because the covariance between random fluctuations in allele frequency is proportional to the same factor ($p_i q_i/2$) as determines the response to selection and mutation (eqn 5), an explicit formula for the equilibrium distribution ψ_0 can be found:

$$\psi_0(\boldsymbol{p})\,\mathrm{d}\boldsymbol{p} = \frac{\mathrm{e}^{2NU}}{VZ}\mathrm{d}\boldsymbol{p}. \tag{10a}$$

This is just Wright's (1935) formula:

$$= \frac{\bar{W}^{2N}}{Z} V^{4N-1}\,\mathrm{d}\boldsymbol{p} \tag{10b}$$

(where $\mathrm{d}\boldsymbol{p} = \prod_{i=1}^{n} \mathrm{d}p_i$).

The potential U, and the corresponding distribution ψ_0, is dominated by sharp peaks at the stable deterministic equilibria. The normalization constant, Z, can be calculated by integrating around each peak, and then summing over peaks:

$$Z = \sum Z_{\underline{m}}, \text{ where } Z_{\underline{m}} = \int_{\text{near } \underline{m}} \mathrm{e}^{2NU}\,\mathrm{d}\boldsymbol{p}. \tag{11}$$

Here, the sum is taken over all distinct equilibria, and the integral is taken around one peak in U. The subscript $\underline{m}$ refers to one particular equilibrium in the class $[m, 0, M]$; N is assumed to be large enough that the peaks are well separated.

The chance that, after a steady state has been reached, the population is near equilibrium $\underline{m}$ is just $Z_{\underline{m}}/Z$. The rate of shifts from the vicinity of one stable equilibrium, through a saddle in U, to a new state, is denoted by Γ. It can be calculated from the equilibrium distribution (Gardiner, 1983, Barton & Rouhani, 1987, eqn 14):

$$\Gamma^{-1} = 2N \int_{\epsilon}\left[\int_{S} \psi_0\,\mathrm{d}\boldsymbol{S}\right]^{-1}\frac{\mathrm{d}\epsilon}{V}. \tag{12}$$

The integration proceeds in two steps. ψ_0 is first integrated across surfaces $\boldsymbol{S}$ which are transverse to the ridge which connects the two stable states, via the saddle; each of these surfaces contains a peak on the ridge. This integral across $\boldsymbol{S}$ is a function of position along the ridge (ϵ), and decreases to a minimum at the saddle. The inverse of this function is then integrated to give the inverse of the transition rate.

Exact integration

It is not easy to evaluate eqns 11 and 12. The integrals involve many degrees of freedom, and so they cannot be calculated numerically, short of direct simulation or related Monte Carlo methods (Hastings, pers.

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comm.). However, in the particular case of an additive character, an exact solution can be found. The problem is simplified by the fact that we are only interested in a few of the many dimensions. For example, we might be interested in the phenotypic mean and variance. If the phenotypic distribution is approximately normal, and if selection acts only on the polygenic character, then the mean fitness depends only on the mean and variance. Therefore, the integral of ψ_0 over allele frequency, conditional on the mean and variance is:

$$\psi_0(z,v) = \bar{W}(z,v)^{2N}\frac{F(z,v)}{Z}, \tag{13}$$

where $F(z,v) = \int V^{4N\mu-1}\,\mathrm{d}\boldsymbol{p}$ (the integral being taken over fixed z,v).

When $4N\mu < 1$, this integral will include many peaks, corresponding to near fixation for different alleles. It can be split into separate components, $F_{\underline{m}}$, as in eqn (11). Equation (13) separates the distribution into a factor reflecting the effects of selection, and a factor $F(z,v)$ which reflects the genetic structure; this latter is just the distribution of phenotype in the absence of selection.

There is a close analogy here with thermodynamics. The function $\bar{W}^{2N}$ is equivalent to the Boltzmann distribution, $\log(\bar{W})$ being analogous to the energy, and $2N$ to $1/kT$, the inverse temperature. The integral over all possible states (eqn 11) gives the partition function, Z. The entropy, S, can be defined by $F = \exp(2NS)$; it is a measure of the number of microscopic states (here, allele frequencies) which give a specified macroscopic state (here, z,v). The distribution of the macroscopic variables (eqn 13) depends on the log mean fitness ('energy') and also on the density of states ('entropy'). One could draw the analogy differently, by equating the whole potential U with the energy, and defining F as $\int V^{-1}\,\mathrm{d}\boldsymbol{p}$; the latter then becomes a purely geometric term. The effects of mutation would then be included with the energy, rather than the entropy. It is not obvious which analogy is more helpful.

Because the trait is assumed to be determined by the sum of effects of the n loci, the distribution in the absence of selection, $F(z,v)$, can be found simply by convolving the separate distributions contributed by each locus. Since we need to know the distribution when the population is in the vicinity of some particular equilibrium of the class $\underline{m}$, F must be divided into its components, $F_{\underline{m}}$. The division is made by dividing each of the n allele frequencies at the appropriate unstable threshold, ρ. Strictly, one should subdivide the allele frequency space into the domains of attraction of the various equilibria; however, the procedure used here will be a good approximation when the populations cluster close to the equilibria.

The convolution can be carried out by a method based on Fourier transformation. We first represent the constraint of fixed z,v by two Dirac delta functions:

$$F_{\underline{m}}(z,v) = \int \delta\left(z - \sum_{j=1}^{n}\alpha(p_j - q_j)\right) \times \delta\left(v - \sum_{j=1}^{n} 2\alpha^2 p_j q_j\right)\prod_{j=1}^{n}\left(\frac{p_j q_j}{2}\right)^{4N\mu-1}\mathrm{d}\boldsymbol{p}. \tag{14a}$$

Since the delta function can be written as $\delta(x) = \int \mathrm{e}^{i\tilde{x}x}\,\mathrm{d}\tilde{x}/2\pi$,

$$F_{\underline{m}}(z,v) = \iiint \frac{\exp\left[i\tilde{z}\left(z - \sum_{j=1}^{n}\alpha(p_j - q_j)\right)\right]\exp\left[i\tilde{v}\left(v - \sum_{j=1}^{n} 2\alpha^2 p_j q_j\right)\right]}{(2\pi)^2} \times \prod_{j=1}^{n}\left(\frac{p_i q_j}{2}\right)^{4N\mu-1}\mathrm{d}\boldsymbol{p}\,\mathrm{d}\tilde{z}\,\mathrm{d}\tilde{v}. \tag{14b}$$

This separates into a product over loci:

$$F_{\underline{m}}(z,v) = \iint \frac{\mathrm{e}^{iz\tilde{z}}\,\mathrm{e}^{-iv\tilde{v}}}{(2\pi)^2} \times (H_{-}(\alpha\tilde{z},\alpha^2\tilde{v}))^m (H_{+}(\alpha\tilde{z},\alpha^2\tilde{v}))^M\,\mathrm{d}\tilde{z}\,\mathrm{d}\tilde{v} \tag{14c}$$

where

$$H_{-}(a,b) = \int_0^{\rho_-} \mathrm{e}^{ia(p-q)}\,\mathrm{e}^{2ibpq}\left(\frac{pq}{2}\right)^{4N\mu-1}\mathrm{d}p \tag{14d}$$

$$H_{+}(a,b) = \int_{\rho_+}^{1} \mathrm{e}^{ia(p-q)}\,\mathrm{e}^{2ibpq}\left(\frac{pq}{2}\right)^{4N\mu-1}\mathrm{d}p. \tag{14e}$$

The functions H_{-}, H_{+} are the Fourier transforms of the allele frequency distributions at loci near fixation for the $-$ or $+$ alleles, respectively. The limits of integration are at the unstable equilibria which must be crossed by loci passing from a $-$ allele to a $+$ allele (ρ_{-}), or by loci passing from a $+$ allele to a $-$ allele (ρ_{+}).

The above derivation uses the fact that the Fourier transform of a convolution is the product of the Fourier transforms of the individual distributions. The method could easily be extended to include dominance, but would be complicated by epistasis. For example, if distinct pairs of loci (i,j) interact, eqn (14*c*) becomes a product over functions H which are two dimensional integrals over p_i and p_j.

Equation 14*d*, *e* is similar to those given by Bulmer (1972), who derived expressions for the expected variance in this model. However, there are two key differences. First, Bulmer assumes that the mean always coincides with the optimum, so that the loci evolve independently. Here, the term $\bar{W}^{2N}$ in eqn (13) introduces a coupling between the loci. Second, Bulmer calculates the overall variance, rather than the variance when the population is near one of the many stable equilibria. Because we are concerned with only a part of the allele frequency space, eqns 14*d*, *e* cannot be solved analytically: Bulmer was able to write the expected variance, averaged over all equilibria, in terms of hypergeometric functions.

Equation 14 can be applied to find the probability

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that the population is near some equilibrium (Z_m/Z), the rate of transition between equilibria (Γ), the marginal distribution of allele frequency ($\tilde{\psi}_0(p)$), and the distribution of phenotypic mean and variance. This method will be referred to below as 'exact integration'; details are given in Appendix 1. The calculations can be speeded up by assuming that $F(z, v)$ is Gaussian. This leads to simple expressions for the distribution of the phenotypic mean and variance (eqn A 1.8–1.10), and will be referred to as the 'partial Gaussian' approximation.

The full Gaussian approximation

Explicit formulae can be obtained by making two approximations. First, assume that $4N\mu$ is large enough that allele frequency distributions at each locus are approximately Gaussian. (This should not be confused with the approximation that allelic effects are normally distributed (Nagylaki, 1986): that clearly cannot be the case here, since there are only two alleles at each locus. Nor should it be confused with the much weaker assumption that the distribution of the phenotype in the absence of selection, $F(z, v)$, is Gaussian – the 'partial Gaussian' approximation).

Second, instead of integrating over fixed (z, v), the average allele frequencies at the m loci near fixation for the $-$ allele ($p = \Sigma p_i/m$) and at the M loci near fixation for the $+$ allele ($P = \Sigma P_i/M$) are fixed. This is less elegant, because it does not lead to a separation between mean fitness and the underlying allele frequencies. However, it does not affect the accuracy of the calculations in this paper. This is because loci will usually be close to fixation, so that (assuming $v = 0$) $v \approx 2\alpha^2(mp + MP)$, and so is approximately fixed. In any case, the integrals will be taken around points where the surface of fixed (z, v) is tangent to the surface of fixed (p, P), and only small fluctuations will be considered. Though one can argue that this 'full Gaussian' approximation is unnecessary, since numerical results can be obtained by exact integration, I include it here because it is widely used to approximate stochastic systems (Barton & Rouhani, 1987), and because it is surprisingly successful, even where the allele frequency distribution is in fact far from Gaussian.

The equilibrium distribution can be found by using eqn (2) to substitute for $\bar{W}$ in eqn (10). The formula separates into three factors. Two of these correspond to the two sets of m and M loci; they are coupled together by the first term, $\exp(-Ns\alpha^2\delta^2)$:

$$\psi_0 = \exp(2NU) = \exp(-Ns\alpha^2\delta^2) \times \exp\left(-2Ns\alpha^2 \sum_{i=1}^{m} p_i q_i\right) \prod_{i=1}^{m} \left(\frac{p_i q_i}{2}\right)^{4N\mu-1} \times \exp\left(-2Ns\alpha^2 \sum_{i=m+1}^{n} p_i q_i\right) \prod_{i=m+1}^{n} \left(\frac{p_i q_i}{2}\right)^{4N\mu-1}. \quad (15)$$

We wish to integrate out $(m-1)+(M-1)$ degrees of freedom, to find the distribution of average allele frequencies (p, P) at the two sets of loci. This reduced distribution is:

$$\tilde{\psi}_0(p, P)\,\mathrm{d}p\,\mathrm{d}P = \exp(-Ns\alpha^2\delta^2)\, I(m, p)\, I(M, P)\,\mathrm{d}p\,\mathrm{d}P \quad (16)$$

where

$$I(m, p) = \int \exp\left(-2Ns\alpha^2 \sum_{i=1}^{m} p_i q_i\right) \prod_{i=1}^{m} \left(\frac{p_i q_i}{2}\right)^{4N\mu-1} \mathrm{d}\boldsymbol{p}.$$

Formally, the integrand in I includes many peaks: the range of integration must be restricted to include only the peak near $p_i = p$. The integral is taken over the $(m-1)$ dimensional region $\Sigma_{i=1}^{m} p_i = mp$.

Suppose that $Ns\alpha^2$ is large enough that fluctuations around $p_i = p$ are small, and I can be approximated by a Gaussian integral. To a first approximation, I is given by the value of the integral at $p_i = p$. Fluctuations around $p_i = p$ can be approximated by a factor $\exp(-w\Sigma(p_i - p)^2/2)$; w is the curvature around the peak, and equals $8n(\mu(1-2pq)/s\alpha^2p^2q^2 - 1)$. The integral of this factor, subject to the constraint $\Sigma(p_i - p) = 0$, is $\sqrt{(2\pi/w)^{m-1}}/m$, and so:

$$I(m, p) = \exp(-2Ns\alpha^2 mpq)\left(\frac{pq}{2}\right)^{4N\mu-1}\left(\frac{2}{pq}\sqrt{\frac{2\pi}{w}}\right)^{m-1}. \quad (17)$$

Equations 16 and 17 now combine to give the distribution of average allele frequencies (p, P). The derivation has been based on the assumption that $Ns\alpha^2$ is large, so that only leading terms in $(1/Ns\alpha^2)$ are needed, and so that the distribution of individual allele frequencies is approximately Gaussian. Given this assumption, the distribution of average allele frequencies must also be Gaussian. Furthermore, we can take the peak of this distribution to be at the deterministic equilibrium; then, eqns (3*b*, 4*a*) show that $w = 2Ns\alpha^2 g/pq$, where g is the eigenvalue of the deterministic equations defined by eqn (4*b*). Integrating out superfluous degrees of freedom:

$$\tilde{\psi}_0(p, P)\,\mathrm{d}P\,\mathrm{d}P = \frac{\exp(2NU)}{Z}\sqrt{\left(\frac{2\pi}{Ns\alpha^2}\right)^{n-2}} \times \left(\frac{1}{g}\right)^{m-1}\left(\frac{1}{G}\right)^{M-1}\mathrm{d}p\,\mathrm{d}P. \quad (18)$$

This joint distribution is applied in Appendix 2 to give expressions for the probability that the population is near some equilibrium (Z_m/Z), the rate of transition between equilibria (Γ), the marginal distribution of allele frequency ($\tilde{\psi}_0(p)$), and the distribution of phenotypic mean and variance.

Simulations

Simulations were run to check these analytic predictions. Ideally, one would use direct Monte Carlo simulations, which would represent each individual, and allow for linkage disequilibrium. However, this is not feasible: many loci must be involved

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before multiple equilibria can coexist, and shifts will occur at a significant rate even when there are many ($\approx 10^4$) individuals. Therefore, simulations only tracked allele frequencies at the n loci. Selection and mutation were represented by the discrete time version of eqn (3a). For intermediate allele frequencies, sampling drift was approximated by a Gaussian white noise with variance $pq/2N$. Where fewer than 10 copies of the rarer allele were present, a Poisson distribution was used.

Runs were begun from some particular deterministic equilibrium: results were not recorded for the first $3/\alpha^2 s$ generations, to allow time for random fluctuations to build up. Each run was continued until a shift to some other state occurred: the time before a shift gives an estimate of Γ^{-1}. Whilst the population remained near the initial state, the distribution of the phenotypic mean and variance, and the allele frequency, were recorded. In most cases, 50 replicates were run from each set of parameters.

Determining when a shift has occurred is delicate. The criterion used was that at least one allele frequency should pass beyond the threshold set by the unstable deterministic equilibrium, for at least $1/3\alpha^2 s$ generations. This is unambiguous when $Ns\alpha^2$ is large; however, when $Ns\alpha^2$ is very small, the distribution does not cluster around distinct attractors. The rate of shifts, measured by the above criterion, does not tend to the neutral substitution rate as N tends to zero: this is because a shift is deemed to occur when an allele frequency passes some intermediate threshold, rather than when a substitution is completed.

5. Results

Choice of parameters

The key parameters are n, the number of loci, $Ns\alpha^2$, a measure of the strength of drift relative to selection on each locus, and $\gamma = \mu/s\alpha^2$, the ratio between mutation and selection. The position of the optimum, relative to the point which would be reached under recurrent mutation alone, has rather little effect (Barton, 1986; compare Tables 1a, b). This is because the deterministic equations eqn (3) depend only on δ: a shift in the optimum can be compensated for by a change in $[m, 0, M]$. The remaining parameters can be scaled out: $s\alpha^2$ sets a characteristic timescale, whilst α sets a scale of measurement for the character. We will therefore concentrate on the effects of $Ns\alpha^2$, n, and γ.

Even with this restriction, there is still a wide range of possibilities. Unfortunately, there is little firm evidence on the mutation rates, population sizes, selection pressures, and numbers of loci which might be found in nature. The problem is exacerbated by the fact that per locus mutation rates seem too low to account for observed levels of quantitative variation (Turelli, 1984). However, some rough guesses can be made. A selection pressure $s \approx 0{\cdot}05/V_e$ is typical of values measured in nature and in the laboratory (Turelli, 1984; though measures are obscured by fluctuations in natural selection (Endler, 1986)). The variance introduced by mutation is $n\mu\alpha^2 \approx 10^{-3}V_e$ per generation. In order to account for high heritabilities ($h^2 \approx \frac{1}{3}$, say) by a mutation/selection balance involving rare alleles, one must have $V_e/2 = V_g = (4n\mu/s)$. The total mutation rate $n\mu$ must thus be $\approx 0{\cdot}00625$. This is consistent with the few measurements of the rate of production of mutations affecting quantitative characters, but is hard to reconcile with estimates of the numbers of loci involved in polygenic variation ($n \approx 20$ upwards; Turelli, 1984, Shrimpton & Robertson, 1988), and per locus mutation rates ($\mu \approx 10^{-5} - 10^{-6}$). The problem increases when one realizes that alleles will tend to be selected against not only because of their effects on the character of interest, but also because of their pleiotropic effects on other characters (Turelli, 1986). However, since the aim of this paper is to investigate the effects of drift on polygenic systems with multiple equilibria, this problem will not be discussed further. Most results will be for the case $n = 100$ loci; the above empirical values then imply that $\gamma \approx 0{\cdot}01$. Lower mutation rates ($\gamma = 0{\cdot}0025$) and fewer loci ($n = 25$) will also be considered. These parameter ranges complement those of Burger *et al.* (1988), who considered much smaller population sizes (mostly $Ns\alpha^2 < 2$), and Hastings (1987), who considered many fewer loci ($n = 8-16$).

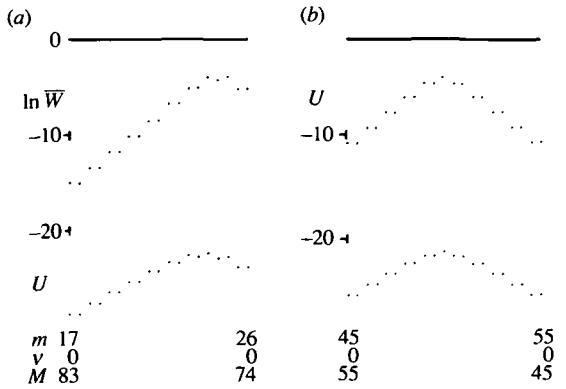

Fig. 1. The log mean fitness ($\log(\bar{W})$) and potential (U) associated with alternative equilibria, for the case $n = 100$, $\gamma = 0{\cdot}01$. (*a*) $z_0 = 5$; (*b*) $z_0 = 0$. The leftmost point in each series corresponds to the most extreme stable equilibrium (*a*) [17, 0, 83]; (*b*) [45, 0, 55]. The next point corresponds to the adjacent unstable equilibrium (*a*) [17, 1, 82]; (*b*) [45, 1, 54]. Stable and unstable equilibria then alternate until the rightmost stable equilibrium is reached.

Distribution across equilibria

The chance that a population will be near to some particular deterministic equilibrium depends primarily on the potential, $U = \log(\bar{W}) + 2\mu\log(V)$. This combines the effects of selection (which tends to increase mean fitness) with the effects of mutation (which tends to increase genetic variance). U is plotted against the possible classes of equilibria in Fig. 1, for

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Table 2. *Comparison of exact integration, and the full and partial Gaussian approximations, for different classes of stable equilibria* $[m, 0, M]$

m	M	Exact integration		Partial Gaussian		Full Gaussian	
(*a*) $Ns\alpha^2 = 10$, $n = 100$, $\gamma = 0{\cdot}01$, $z_0 = 0$							
45	55						−7·589
46	54			−9·113	−5·754	−1·704	−5·652
47	53	0·00000	0·00010	−9·227	−5·805	0·00012 −7·654	−5·180
48	52	0·00000	0·00299	−9·222	−5·805	0·00156 −9·192	−5·132
49	51	0·05998	0·09651	−8·093	−5·982	0·09546 −7·946	−5·832
50	50	0·88004	0·80081	−8·093	−5·982	0·80572 −7·946	−5·832
51	49	0·05998	0·09651	−9·222	−5·805	0·09546 −9·192	−5·132
52	48	0·00000	0·00299	−9·227	−5·805	0·00156 −7·654	−5·180
53	47	0·00000	0·00010	−9·113	−5·754	0·00012 −1·704	−5·652
54	46						−7·589
55	45						
(*b*) $Ns\alpha^2 = 20$, $n = 100$, $\gamma = 0{\cdot}01$, $z_0 = 0$							
45	55						−7·589
46	54			−11·824	−9·639	−13·131	−5·657
47	53			−12·544	−9·440	−18·222	−5·230
48	52			−14·627	−8·334	−17·796	−5·403
49	51	0·00462	0·00978	−12·424	−7·817	0·00357 −12·717	−7·109
50	50	0·99077	0·98045	−12·424	−7·817	0·99285 −12·717	−7·109
51	49	0·00462	0·00978	−14·627	−8·334	0·00357 −17·796	−5·403
52	48			−12·544	−9·440	−18·222	−5·230
53	47			−11·824	−9·639	−13·131	−5·657
54	46						−7·589
55	45						
(*c*) $Ns\alpha^2 = 10$, $n = 100$, $\gamma = 0{\cdot}0025$, $z_0 = 0$							
48	52			−10·795		−6·004	−4·148
49	51	0·00011	0·08289	−10·362	−8·053	0·00305 −5·633	−11·400
50	50	0·99988	0·83422	−10·362	−8·053	0·99390 −5·633	−11·400
51	49	0·00011	0·08289	−10·795		0·00305 −6·004	−4·148
52	48						
(*d*) $Ns\alpha^2 = 10$, $n = 25$, $\gamma = 0{\cdot}01$, $z_0 = 0$							
12	13	0·5000	0·5000	−6·138	−6·138	0·5000 −6·068	−6·068
13	12	0·5000	0·5000			0·5000	

The third column gives the probability that the population will be in some equilibrium of a class: this includes the factor $[n!/m!M!]$, which is the number of equilibria in the class, and is calculated by exact integration. The fourth column gives this probability, calculated using the partial Gaussian approximation. The fifth and sixth columns give the log transition rates ($\log(\Gamma)$) either away from the optimal equilibrium, or towards it (fifth and sixth columns, respectively); these rates are scaled relative to the characteristic time $2/s\alpha^2$. These values are calculated using the partial Gaussian approximation. The last three columns give corresponding predictions from the full Gaussian approximation.

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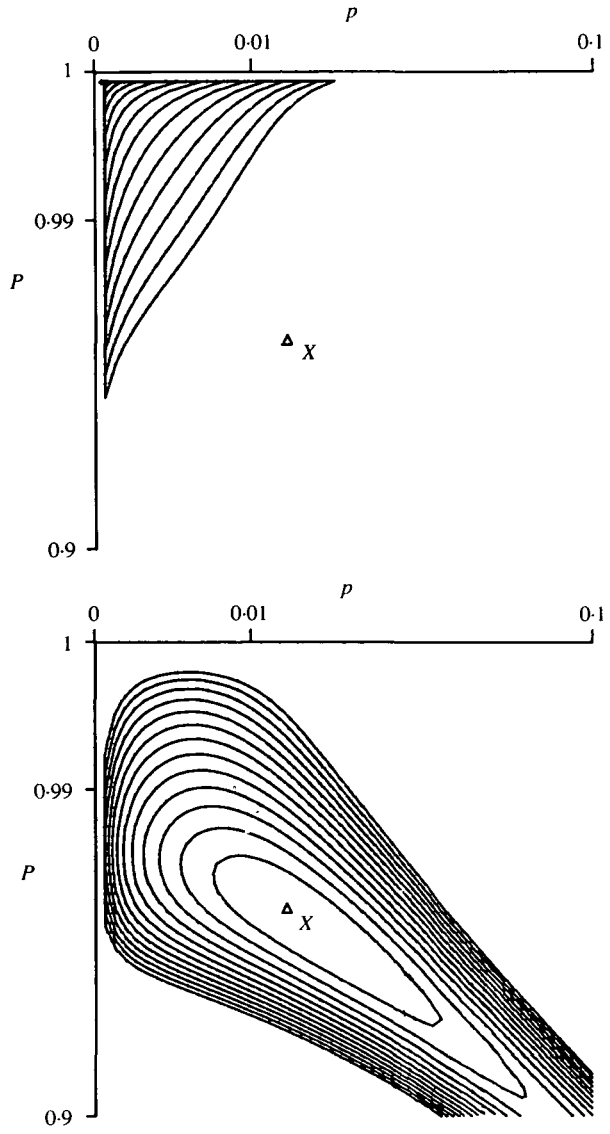

Fig. 2. (*a*) The logarithm of the equilibrium probability distribution of two particular allele frequencies, one chosen from the set of m loci at low frequency (p_i), and one from high frequency (P_i). All other loci are held at the deterministic equilibrium. The distribution is plotted on an arc–sin transformed geodesic scale. $z_0 = 0$, $Ns\alpha^2 = 10$, $\gamma = \mu/s\alpha^2 = 0{\cdot}01$, $n = 100$; hence, $4N\mu = 0{\cdot}4$ is small enough that the distribution rises to a singularity at $p = 0$, $P = 1$. Contours are spaced at 0·1 units of log probability. (*b*) The distribution of average allele frequencies, (p, P), for the same case. Here, contours are spaced 10 units of log probability apart: the distribution is tightly clustered around the peak (Δ). The deterministic equilibrium (X) is slightly displaced from the peak.

the standard parameter set ($n = 100, \gamma = 0{\cdot}01$). Values of U, and of log mean fitness, are also given in Table 1. Note that the pattern of log mean fitness parallels the potential: thus, the most likely state also has highest mean fitness.

The graph of U against possible equilibria consists of a series of rectangular steps; the drop in potential which impedes transitions away from the optimal equilibrium is much greater than the drop which impedes shifts in the opposite direction. Indeed, the latter barrier is barely visible in Fig. 1. We therefore expect that over a wide range of population sizes, drift will be strong enough to knock the population away from suboptimal states, but not strong enough to knock it away from the optimal state. The population size at which drift allows shifts at an appreciable rate across a barrier ΔU is $N \approx 2/\Delta U$. When $z_0 = 0$ (Fig. 1*b*), escape from equilibria [50, 0, 50], [49, 0, 51], [48, 0, 52], ...becomes likely when $Ns\alpha^2 < 8{\cdot}4$, 31·3, 156·0, 784·3, ...If, as is likely, selection on each locus is weak, these figures correspond to large numbers of individuals: taking the rough estimates of the previous section, if $s\alpha^2 \approx 4 \times 10^{-4}$, then the criterion for stability is that $N < 21{,}000$; 78,000; 369,000; 1,961,000....

The chance that the population lies near the optimal state depends on the shape of the distribution ($\exp(2NU)$) near that state, as well as on the height of the peak in U. It can be calculated by integrating around the peak, using either the exact method, or the Gaussian approximation (eqn 23). Both give similar results (Table 2), confirming that provided $Ns\alpha^2 > 2$, the population is most likely to be found near the deterministic equilibrium in which the mean is closest to the selective optimum. Calculations of transition rates (see below) also show that shifts towards the optimum are (for $Ns\alpha^2 > 2$) more frequent than those away from it, and that these shifts can be frequent enough, even in a large population, for the optimum to be reached quickly (Fig. 6).

Distribution of allele frequencies

Calculations of transition rates, and of phenotypic distributions, depend on averaging over irrelevant variables. This procedure is illustrated in Fig. 2. Here, population size is small enough that the distribution of individual allele frequencies is strongly skewed: it rises to a singularity at fixation. The distribution illustrated in Fig. 2*a* is a cross-section through an n-dimensional hypercube, with peaks at every corner. This n-dimensional distribution of average allele frequencies is reduced to a two-dimensional distribution of average allele frequencies ($\tilde{\psi}_0(p, P)$; eqns 16, 18). Figure 2*b* shows that this latter is tightly clustered around the deterministic equilibrium and has an approximately Gaussian form near the peak. Simulations confirm that although individual allele frequencies vary widely, their averages follow the distribution of Fig. 2*b*.

By integrating over all but one allele frequency, the marginal distribution at each locus can be found. The distributions at loci almost fixed for '+' alleles, and for loci almost fixed for '−' alleles, are shown on the same graph in Fig. 3. The theoretical distribution (whether calculated by exact integration, by the partial Gaussian approximation, or by the full Gaussian approximation) is indistinguishable from simulation results on this scale.

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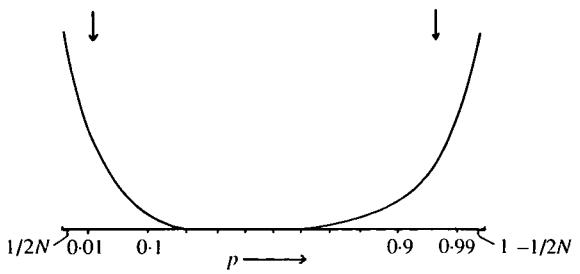

Fig. 3. The distribution of allele frequency ($\tilde{\psi}_0(p)$), given that the population is near [49, 0, 51]. $n = 100$, $\gamma = 0{\cdot}01$, $Ns\alpha^2 = 10$, $z_0 = 0$. p is plotted on an arc–sin transformed scale. The left-hand curve shows the marginal distribution for the 49 loci nearly fixed for '−'; the right-hand curve is for the 51 loci nearly fixed for '+'. The two arrows show the deterministic equilibria. Simulation results (from 64,000 generations) are drawn on the same graph, and are indistinguishable from the theoretical prediction, except at extreme frequencies: when $p < 1/2N$ or $p > 1-1/2N$, the diffusion approximation breaks down. (Here and in Fig. 2, the distribution is calculated using the full Gaussian approximation. Results from the partial Gaussian approximation and from exact integration are indistinguishable.)

Transition rates

Theoretical calculations of transition rates are compared in Fig. 4, for the standard case of $n = 100$, $\gamma = 0{\cdot}01$, $z_0 = 0$. Even though the distribution of allele frequencies is strongly skewed when $Ns\alpha^2 < 20$ (Figs. 2*a*, 3), the full Gaussian approximation (straight solid line in Fig. 4) is close to the partial Gaussian approximation for $Ns\alpha^2 > 5$ (dotted solid line in Fig. 4). Results from exact integration are not given, because they require calculation of a three-dimensional integral. However, they should be close to the partial Gaussian approximation: the distribution across equilibria, and the marginal distribution of allele frequencies, from these two methods are similar (Table 2).

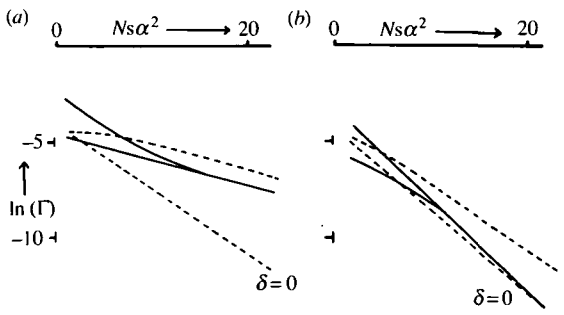

Fig. 4. Comparison of various approximations to the transition rate, Γ. This is the chance per generation of a shift from the vicinity of one particular state to the vicinity of another particular state. (Since there are many neighbouring states, the total transition rate is much higher.) In both graphs, $z_0 = 0$, $n = 100$, $\gamma = 0{\cdot}01$. (*a*) [49, 0, 51] to [50, 0, 50]. (*b*) [50, 0, 50] to [49, 0, 51]. Results from exact integration are shown by the solid curve; the Gaussian approximation is shown by the solid straight line, and coincides with exact integration for $Ns\alpha^2 > 8$. The dotted lines show two single locus approximations. The line $\delta = 0$ is obtained by ignoring deviations from the optimum; it is the same in (*a*, *b*). The other dotted line is obtained by linear interpolation of the deviation, δ.

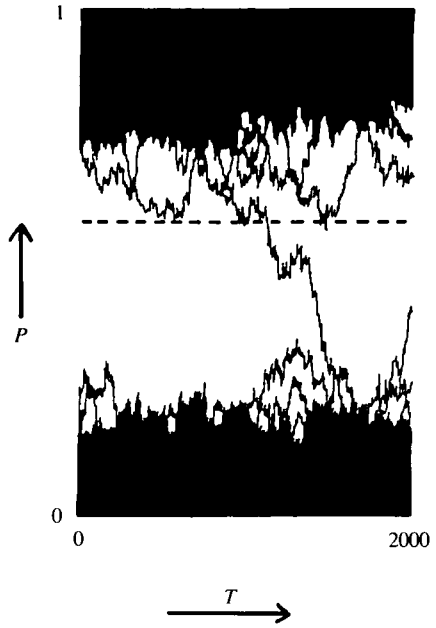

Fig. 5. A typical segment of a simulated path. $Ns\alpha^2 = 10$, $\gamma = 0{\cdot}01$, $n = 100$, $s = 1$, $\alpha = 0{\cdot}1$, $z_0 = 0$. The population begins at a deterministic equilibrium of class [49, 0, 51], and runs until a shift to [50, 0, 50] occurs (downward line on right). The graph shows allele frequencies at the 100 loci, plotted on an arc–sin transformed scale.

Two single-locus approximations are also shown, by dotted lines. Ignoring deviations from the optimum altogether (i.e., $\delta = 0$) gives a model of symmetric underdominance. This gives poor results: it predicts equal rates for all classes of equilibria, when in fact the optimal equilibrium [50, 0, 50] is much stabler. Linear interpolation of δ between the deterministic equilibria gives better results; however, there is still a substantial discrepancy, which is due to the failure to account for fluctuations at the $(n-1)$ loci which are not directly involved in the shift.

These various predictions can be checked against simulations. Figure 5 shows a typical run. Allele frequencies fluctuate near fixation. Occasionally, one allele frequency drops to hover near the unstable threshold (dotted line), and then either returns to its original state or drops further. The average time before a shift from $[m, 0, M]$ to $[m-1, 0, M+1]$ gives an estimate of $(1/M\Gamma)$; the factor M is introduced because M loci are liable to shift from '+' to '−'.

For the standard case, with $\gamma = 0{\cdot}01$, the partial Gaussian approximation gives results in good agreement with the simulations over the whole range of $Ns\alpha^2$ for shifts from [49, 0, 51] to [50, 0, 50] (Fig. 6*a*). For jumps in the opposite direction, agreement is less good (Fig. 6*b*). This is to be expected, since the analytic predictions are based on a formula derived for large $Ns\alpha^2$ (eqn (12)). When populations are small, some disagreement is to be expected: allele frequencies

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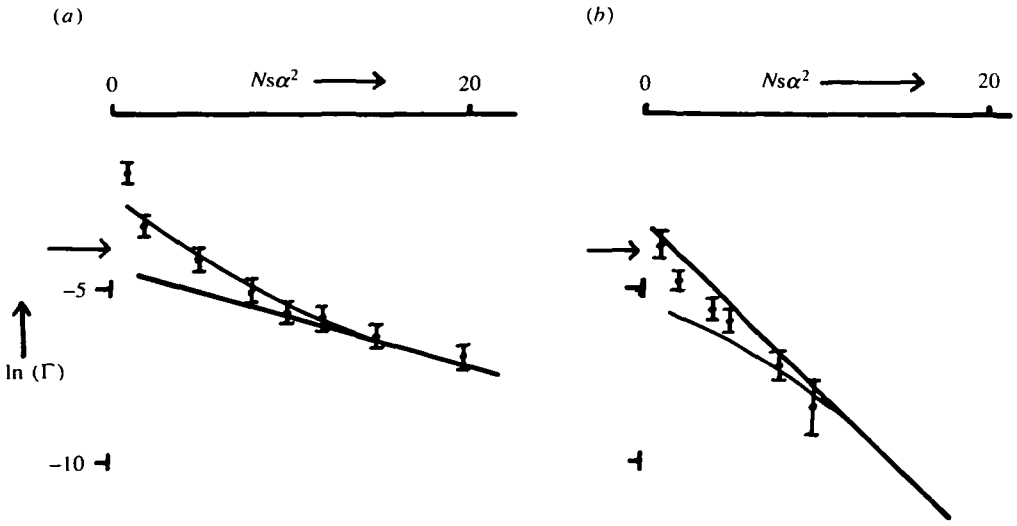

Fig. 6. Comparison between exact integration (solid curve), the Gaussian approximation (solid straight line), and simulation results. Parameters are as for Fig. 4, except that N is varied. For each value of N, simulations were run until 50 shifts had occurred (excepting the rightmost points in Fig. 5*b*, where only 7 shifts were seen). The bars show $\log(\Gamma) \pm 2$ standard errors. The arrow on the left of each graph shows the neutral substitution rate (μ).

fluctuate so much that it is not clear when the population is 'near' one or other deterministic equilibrium, and the simulation results become sensitive to the criteria used to define a shift.

The full Gaussian approximation (straight lines in Figs. 6*a*, *b*). is good for $Ns\alpha^2 > 5$, and performs almost as well as the results from exact integration. This is surprising, since the distribution of allele frequencies is strongly skewed (Fig. 3). The unreasonable accuracy of the full Gaussian approximation is a common, and as yet unexplained phenomenon; it arises, for example, in quantum mechanics and in optics (Schulman, 1981, Ch. 5).

The arrows in Fig. 6 show the neutral substitution rate ($\Gamma = \mu$), which is expected when $Ns\alpha^2$ is small enough that selection is negligible. Simulations at small N give rather higher rates. There are two reasons for this. First, the definition of a shift is that

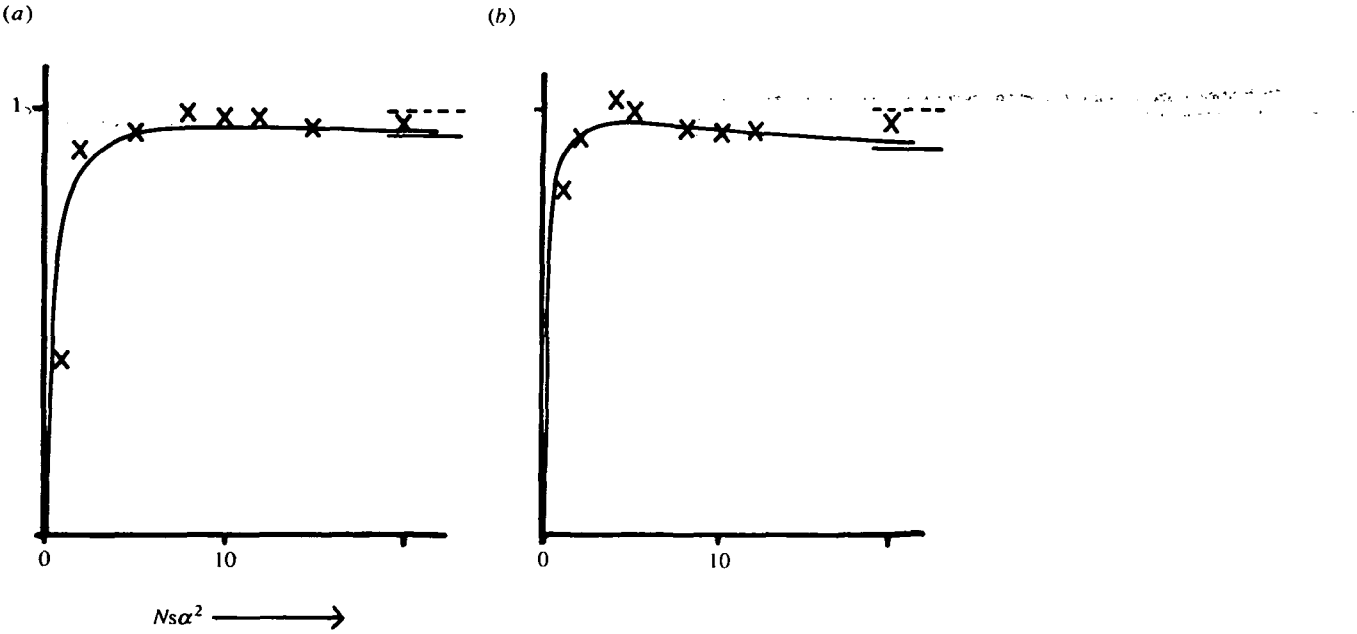

Fig. 7. The variance of the phenotypic mean, plotted as $2Ns.\mathrm{var}(z)$, against $Ns\alpha^2$. $z_0 = 0$, $n = 100$, $\gamma = 0{\cdot}01$, $s = 1$, $\alpha = 0{\cdot}01$. (*a*) [49, 0, 51]; (*b*) [50, 0, 50]. Crosses show simulation results. The naive phenotypic prediction (eqn 8*a*) is that this quantity is always equal to 1 (dotted line on right). The full Gaussian approximation predicts a somewhat lower constant value (solid line on right, from eqn A 2.2*b*). The solid curve shows the prediction from exact integration, which is very close to the partial Gaussian approximation.

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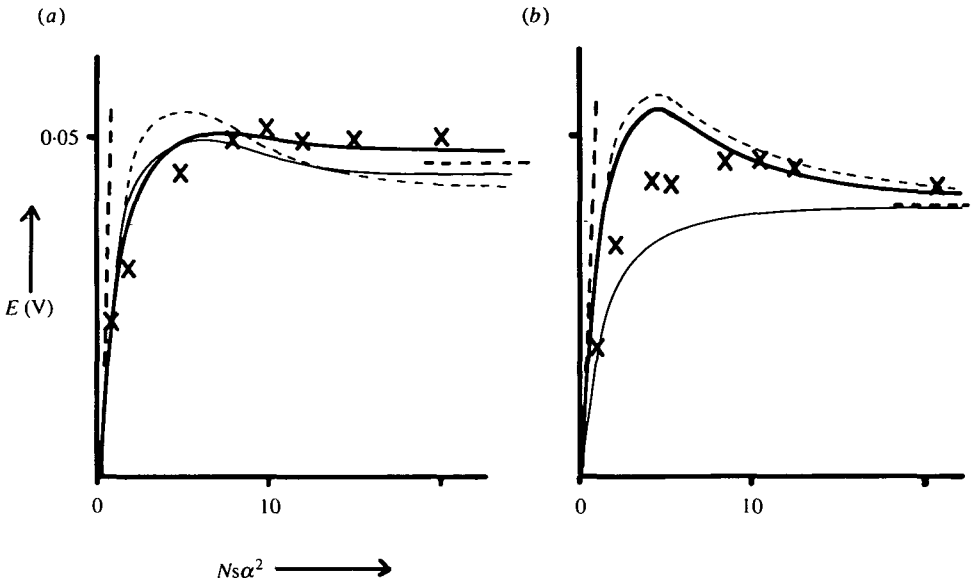

Fig. 8. The expected phenotypic variance, plotted against $Ns\alpha^2$. Parameter values are as for Fig. 7. Crosses show simulation results (*a*) [49, 0, 51]; (*b*) [50, 0, 50]. The right-hand horizontal dotted line gives the deterministic equilibrium, which is slightly higher for the asymmetric equilibrium (*a*). The left-hand dotted line gives the neutral prediction ($v = 4Nn\mu$). The heavy solid curve shows the prediction from exact integration. The light dotted curve shows the prediction obtained by neglecting variations about the optimum (which is close to Bulmer's (1972) formula). The light solid curve in (*a*) shows the prediction from the partial Gaussian approximation. For the symmetric equilibrium (*b*), this is indistinguishable from exact integration, and so is not shown: there, the light solid curve shows the Gaussian approximation (eqn A 2.2*a*).

allele frequency should pass some intermediate threshold, rather than that a substitution should occur. When $Ns\alpha^2$ is large, a locus that passes the threshold will almost certainly go on to near fixation for the new allele (cf. Fig. 5). However, when $Ns\alpha^2$ is small, frequencies may often return to their original values. Second, though selection opposes the initial increase of a rare allele, it assists the shift once the threshold is passed. This may increase the rate of shifts above the neutral rate when the initial equilibrium is asymmetric (compare Figs. 6*a*, *b*).

Distribution of the phenotype

The variance of the mean around the deterministic equilibrium is shown in Fig. 7, as a function of population size. The product $2Ns.\mathrm{var}(z)$ is plotted; naive phenotypic arguments predict that this should have a constant value of 1 (eqn 8*a*). The variance is indeed close to this prediction (upper dotted line) provided that the population is not too small ($Ns\alpha^2 > 1$). If allele frequencies follow a multivariate Gaussian distribution, $2Ns.\mathrm{var}(z)$ should have a somewhat smaller value (lower solid line; eqn A 2.2*b*). The more sophisticated prediction, from exact integration, is shown by the solid curve: this converges to the full Gaussian prediction as $Ns\alpha^2$ becomes large, and the underlying distributions approach normality. The main conclusion is that the mean is never likely to deviate from the optimum by more than $\approx \sqrt{2/Ns}$ for $Ns\alpha^2 > 1$. Since $Ns\alpha^2 \mathrm{var}(z)$ decreases for small N, this limit may always hold: it implies that the 'drift load' which arises from deviations from the optimum is $\leqslant 1/4N$.

The relation between the genetic variance and population size is shown in Fig. 8. The variance is somewhat higher when the population is near an asymmetric equilibrium in the class [49, 0, 51] (Fig. 8*a*). Since drift is likely to keep the population near to the optimal state [50, 0, 50], we should concentrate on Fig. 8*b*. The variance is close to the deterministic value (right hand dotted line) for $Ns\alpha^2 > 2$. It decreases to zero as the population becomes very small; however, selection holds the variance well below the neutral prediction ($v = 2nNs\mu$; left hand dotted line), even for small N. Surprisingly, the variance increases slightly for intermediate $Ns\alpha^2$ before decreasing in very small populations. This effect was predicted by Bulmer (1972), by integration of the single-locus distribution on the assumption that the mean coincided with the optimum (dotted curve). Exact integration of the multilocus distribution, or use of the partial Gaussian approximation, gives results similar to Bulmer's, showing that fluctuations in the mean have little effect on the variance. However, the full Gaussian prediction (shown in Fig. 8*b* by the lower solid curve) does not predict this increase. Simulations do show an increase at intermediate $Ns\alpha^2$. However, it is smaller than predicted for the symmetric equilibrium (Fig. 8*b*). The reason for this discrepancy is obscure: it may be an artefact of the criterion used to decide when the population has shifted to a new equilibrium.

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Accumulation of reproductive isolation

Suppose that two isolated populations each remain in a balance between mutation and stabilizing selection. Even though both are subject to the same selection pressures, and the mean in both may remain close to the same optimum, drift will occasionally change the underlying combination of alleles. Eventually, the combination may become different enough that when the populations cross, extreme and unfit recombinants will be produced. To find the rate at which reproductive isolation will evolve, we must know first, the level of isolation produced when populations differ at k/n loci, and second, the rate at which they become different.

In a large population at equilibrium, in which the mean coincides with the optimum, the genetic variance is $v = 4n\mu/s$. This reduces mean fitness by $sv/2 = 2n\mu$. We can compare levels of isolation with this basic mutation load. In the extreme case, suppose that two populations differ in the common allele at all n loci. Then, the F1 population will have intermediate phenotype, and will be slightly fitter than either parent. However, in the F2 population, all loci will have equal allele frequencies; this gives a variance $(2n\alpha^2pq) = (n\alpha^2/2)$. The log mean fitness is therefore reduced by $sn\alpha^2/4$. In fact, even after indefinite divergence, only half the loci will differ on average; the maximum load in the F2 population is therefore $(sn\alpha^2/8)$. When k loci differ, the load is $(sk\alpha^2/4)$. For example, with the standard values $s\alpha^2/2 = 1/250$, $\gamma = 0{\cdot}01$, $\mu = 8 \times 10^{-5}$, and $n = 100$, the equilibrium load is 0·016, and the maximum reduction in fitness in the F2 is 0·10. This is hardly enough to cause a significant barrier to gene exchange; however, if similar processes were to occur for many characters, substantial isolation could evolve. A limit is placed by the total mutation load, which cannot be very large ($< 0{\cdot}5$, say). With $\gamma = 0{\cdot}01$, the maximum isolation cannot be greater than $(0{\cdot}1/0{\cdot}016) \approx 6$ times this load (< 3, say). In general, the ratio is $(1/16\gamma)$. Thus, if the alleles responsible for polygenic variation are usually rare ($\gamma \ll 1$), substantial isolation could eventually develop.

How rapidly would isolation evolve under stabilizing selection? Shifts away from the optimal equilibrium become most unlikely when $Ns\alpha^2 > 10$; when $Ns\alpha^2 < 2$, the frequency of shifts approaches the neutral rate, μ, per locus. The neutral value sets a rough upper limit on the rate of divergence. This limit is low: for the above values, the maximum isolation of $\approx 0{\cdot}1$ per character develops over a time $\approx 1/\mu =$ 12,500 generations. Mutation rates are in fact likely to be lower than the value of 8×10^{-5} used here.

One might imagine that occasional founder events could accelerate speciation. This would be so if the standing populations were so large that stochastic shifts were essentially impossible ($Ns\alpha^2 > 10$, say). However, consider the consequences of the most drastic founder event, in which one haploid genome founds a new population. Then, the chance that the rarer allele at a locus is fixed is equal to its initial frequency, $p \approx 2\gamma$. Therefore, only a small fraction 2γ of the maximum isolation is likely to evolve; this fraction is $\frac{1}{4}$ of the equilibrium mutation load (Barton, 1989). With the above values, a founder event gives isolation of 0·002 per character. Changes during a founder event depend on initial polymorphism: here, levels of polymorphism at each locus are low.

The most plausible cause of reproductive isolation under this model of polygenic variation seems to be a combination of a fluctuating optimum and weak sampling drift. First, consider slow changes in the optimum in an infinite population. Because a wide range of equilibria are stable, shifts between different combinations of common alleles would not occur: the mean would instead be adjusted to the optimum by slight changes in allele frequency, at the cost of an increase in genetic variance. For example, with $n = 100$, $\gamma = 0{\cdot}01$, changes in optimum of as much as $\pm 10\alpha$ do not cause instability: this corresponds to $\pm 3{\cdot}3$ phenotypic standard deviations. However, drift will knock even a fairly large population away from suboptimal states. So, suppose that the optimum shifts by 2α, or 0·66 standard deviations, in a finite population. If $Ns\alpha^2 < 20$, a shift to the new optimal equilibrium is likely to occur within $\approx 1/m\Gamma$ generations (3,000 generations; Fig. 6*a*). Rapid fluctuations would have the same effect as sampling drift, and would promote rather slower isolation (see Maynard Smith, 1979).

6. Discussion

We can now return to the general questions raised in the introduction. First, can the evolution of polygenic variation be understood from gross phenotypic measures, without detailed knowledge of processes at individual loci? In an infinite population, many different equilibria with different properties may coexist. Thus, the state of the population cannot be predicted without knowing which of these equilibria it has reached. Sampling drift provides one mechanism for crossing between equilibria: over a wide range of population sizes, drift is likely to bring the population close to the optimal state, in which the mean coincides with the selective optimum. Furthermore, provided the population is not extremely small ($N < s\alpha^2 \approx 100$, say), the mean and variance will have a distribution close to that predicted from phenotypic arguments (eqn 8). This is consistent with the simulation results of Burger *et al.* (1988). These conclusions can be phrased in terms of the general results of Barton & Turelli (1987), who showed that changes in the mean and variance depend on the third moment of the distribution of breeding values. Different stable equilibria correspond to different values of the third moment: sampling drift acts to keep the third moment near to zero.

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So, given this model of a set of identical biallelic loci, the existence of multiple equilibria does not cause difficulties in any but very large populations. However, we may still ask whether this conclusion holds for more realistic models of polygenic variation. Obvious extensions are to allow for dominance (Charlesworth *et al.* 1987), for different effects (α_i) across loci, for multiple alleles, and for selection on a vector of quantitative characters. Although a full analysis is needed, one can use dimensional arguments to show that drift will be able to bring the population near to the optimal equilibrium if $N > 1/s\alpha^2$. However, it is the step-like pattern of log mean fitness and potential across equilibria (Fig. 1) which allows the optimal state to be reached across a very wide range of N; it is not clear whether more general models would also show this behaviour, or whether it is an artefact of the extreme symmetry in this model. Numerical results allowing different effects (α_i) across loci show that the mean fitness of different classes of equilibria become more similar to each other.

Of course, polygenic variation may not be maintained by a balance between mutation and stabilizing selection. Other possibilities are that deleterious alleles are maintained by mutation, and have pleiotropic effects on quantitative characters; that polymorphisms maintained by balancing selection have pleiotropic side-effects (Gillespie, 1984*a*); or, that frequency-dependent selection acts directly on the character of interest, so as to maintain variation (Slatkin, 1979). One should note, though, that the main objection to a balance between mutation and stabilizing selection is that an unreasonably high net mutation rate ($n\mu$) is needed to offset the strong stabilizing selection which seems prevalent. Strong stabilizing selection on many characters is hard to reconcile with *any* model since it implies a high genetic load, and a high variance in fitness.

Clearly, the above calculations of the relation between phenotypic distribution and population size may only apply under the specific model used here. However, conclusions about the way optima are reached, and the rate of peak shifts, may apply under more general schemes. As Wright (1932, 1980) has stressed, the prevalence of pleiotropy and epistasis makes multiple equilibria inevitable. This is confirmed by a range of models of multilocus selection (Karlin, 1979). Kaufmann & Levin (1987) have discussed the geometry of systems with multiple local optima, stressing the point that only a tiny fraction of possible gene combinations can be reached from any one genotype (c.f. Gillespie, 1984*b*). In the model discussed here, this fraction is $n/2^n$, which is 8×10^{-29} for $n = 100$. Kaufmann & Levin find that the maximum advance in fitness, from some arbitrary starting point up to the nearest local peak, increases substantially with the correlation in fitness values between adjacent points. The model here is set in a rather different framework from that considered by Kaufmann & Levin: one must consider the surface of U, plotted against all the allele frequencies p_i, rather than considering the fitnesses of individual genotypes (see Provine, 1986, for discussion of this distinction). However, because the population clusters around one genotype, the same considerations apply. It may be that advance towards the global optimum is relatively easy, because the model of additive gene effects leads to a strong correlation between adjacent fitness values. Important areas for future work are to find how far Kaufmann & Levin's arguments apply at the level of populations as well as genotypes, and how far the relative ease with which the global optimum is reached can be related to general features of the model.

How does strong selection on a polygenic character affect individual loci? The rate of shifts approaches that for a neutral locus when $N < 1/s\alpha^2$; it is in this range that drift begins to reduce the phenotypic variance appreciably (compare Figs. 6, 8). It is therefore not possible to reconcile effectively neutral evolution at each locus with strong stabilizing selection, as argued by Kimura (1981, 1983), unless drift has a noticeable effect at the phenotypic level. However, the distribution of allele frequencies is indistinguishable from that for mildly deleterious alleles, for all population sizes. It is therefore not possible to use allele frequencies to distinguish the present model from a version of the neutral theory that incorporates weak purifying selection. One might imagine that the pattern of substitutions would be more helpful. When a single class of equilibria coincides with the selective optimum (Fig. 1*b* rather than Fig. 1*a*), then a shift from an optimal to a suboptimal equilibrium will be quickly followed by a compensating shift in the opposite direction. However, the compensation will be at a different locus, and so will not be reflected by an increased variance of substitution rates (cf. Gillespie, 1986). It is hard to see how observations of individual loci can distinguish stabilizing selection on a polygenic system from simple purifying selection.

Given sufficient time, significant reproductive isolation can evolve between isolated populations subject to the same regime of stabilizing selection. However, the maximum isolation that can evolve can only greatly exceed the mutation load in a standing population when the alleles responsible for variation are extremely rare. Moreover, divergence is extremely slow, at best occurring over a timescale set by the mutation rate. Founder events do not help much, because the alleles responsible for variation are rare, and are likely to be lost rather than fixed. Divergence would be possible in a geographically structured population if the number of individuals exchanged between demes, or the neighbourhood size, were small in at least some times and places ($Nm < 1$, or $4\pi\rho\sigma^2 < 10$; Rouhani & Barton, 1987). However, divergence would still be slow. The most favourable conditions for the evolution of isolation under this

model may be when a fluctuating optimum is combined with weak sampling drift.

These conclusions in fact apply to a wide range of models (Barton & Charlesworth, 1984, Rouhani & Barton, 1987, Barton, 1989). Substantial reproductive isolation is unlikely to evolve rapidly as a result of drift; founder events are only likely to lead to strong isolation through shifts at highly polymorphic loci, and is limited by the standing genetic load; and processes other than pure drift may cause faster speciation. Of course, speciation is a slow process: for example, Coyne & Orr (1989) estimate that sibling species of *Drosophila* diverged, on average, 5 million years ago. Gradual divergence under stabilizing selection may therefore be a major cause of reproductive isolation: as a hypothesis, it has the advantage that the rate of divergence can be calculated from observable features of present-day populations.

This discussion of adaptation and speciation has rested on a simple, symmetrical, and probably unrealistic model. However, the methods used can readily be generalized to other cases. Even using the Gaussian approximation, integration over fluctuations around the equilibria gives accurate predictions, even where the underlying distribution is strongly skewed. It would be interesting to apply these methods to other models to find whether the conclusions of this paper are generally valid.

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Appendix 1. Details of exact integration, and the partial Gaussian approximation

Distribution across equilibria

The chance that the population is near some equilibrium $\underline{m}$ is proportional to $Z_{\underline{m}} = \int \bar{W}^{2N} F_{\underline{m}}(z, v)\,dz\,dv$ (from eqn 13). Substituting for $\bar{W}$ from eqn (2) and for $F_{\underline{m}}$ from eqn (14*c*) we see that the integral over z gives the Fourier transform of a Gaussian (another Gaussian), and the integral over v gives the Fourier transform of an exponential (a delta function). Thus:

$$Z_{\underline{m}} = \int \frac{e^{-i\tilde{z}z_0} e^{-\tilde{z}^2/4Ns}}{\sqrt{(2\pi . 2Ns)}} (H_-(\alpha\tilde{z}, iNs\alpha^2))^{\underline{m}} \times (H_+(\alpha\tilde{z}, iNs\alpha^2))^M \,d\tilde{z}. \quad \text{(A 1.1)}$$

A close approximation to this expression can be obtained by noting that:

$$H_-(\alpha\tilde{z}, iNs\alpha^2) = \int_0^{p_-} (pq/2)^{4N\mu-1} e^{i\alpha\tilde{z}(p-q)} \times e^{-2Ns\alpha^2 pq}\,dp. \quad \text{(A 1.2)}$$

This is the Fourier transform of the allele frequency distribution which would obtain at each locus if the mean always coincided with the optimum: this distribution is given by eqn (26) of Bulmer (1972). (Strictly, H_- is the Fourier transform of the distribution of $\alpha(p-q)$.) Now the product of the Fourier transforms of a set of distributions is the Fourier transform of the convolution of those distributions. The product $H_-^m H_+^M$ is therefore the Fourier transform of the distribution of the phenotypic mean ($z = \Sigma\alpha(p-q)$) which would obtain if fluctuations from the optimum had no effect; this distribution will be denoted by a tilde, ˜. (It would be found if stabilizing selection were centred on the actual mean in each generation, and so tended to reduce the variance without introducing any directional component.)

With a large number of loci, we expect this distribution to be approximately Gaussian, and so characterized by its mean and variance ($\tilde{E}(z)$, $\widetilde{\mathrm{var}}(z)$). In other words, its Fourier transform $H_-^m H_+^M$ should be approximated by a Taylor series expansion around $\tilde{z} = 0$. Since $\partial \log(H_-^m H_+^M)/\partial\tilde{z} = i\tilde{E}(z)$, and $\partial^2 \log(H_-^m H_+^M)/\partial\tilde{z}^2 = -\widetilde{\mathrm{var}}(z)$ (from eqn 14*d*, *e*), we have:

$$(H_-(\alpha\tilde{z}, iNs\alpha^2))^{\underline{m}} (H_+(\alpha\tilde{z}, iNs\alpha^2))^M \approx (H_-(0, iNs\alpha^2))^{\underline{m}} (H_+(0, iNs\alpha^2))^M \times \exp(i\tilde{z}\tilde{E}(z)) \exp(-\tilde{z}^2 \widetilde{\mathrm{var}}(z)/2). \quad \text{(A 1.3)}$$

Substituting into eqn (A 1), and integrating across $\tilde{z}$:

$$Z_{\underline{m}} = \frac{(H_-(0, iNs\alpha^2))^{\underline{m}} (H_+(0, iNs\alpha^2))^M}{\sqrt{1 + 2Ns\,\widetilde{\mathrm{var}}(z)}} \times \exp\left(-\frac{(\tilde{E}(z) - z_0)^2 Ns}{(1 + 2Ns\,\widetilde{\mathrm{var}}(z))}\right). \quad \text{(A 1.4)}$$

The 'partial Gaussian' approximation used here, that $H_-^m H_+^M$ is roughly Gaussian in $\tilde{z}$, is much weaker than the full 'Gaussian approximation' discussed above and in Appendix 2, that allele frequencies at individual loci are normally distributed. For the parameter values used in this paper, eqn (A 1.4) is usually close to the exact result, eqn (A 1) (Figs. 7, 8).

The marginal distribution, and transition rates

Consider one locus, with allele frequencies u, v. If $(m-1)$ of the other loci are near fixation for the '$-$' allele, and M are near fixation for the '$+$' allele, then the population will be close to an equilibrium in the class $[m, 0, M]$ when u is small, and will move towards $[m-1, 0, M+1]$ as u increases. For given u, the distribution of the remaining $(n-1)$ allele frequencies will be as if the optimum were at $(z_0 - \alpha(u-v))$. Hence, the integral over these $(n-1)$ variables will be given by eqn (A 1.4) evaluated for this shifted optimum, and for an equilibrium in the class $[m-1, 0, M]$:

$$\tilde{\psi}_0(u) = \left(\frac{uv}{2}\right)^{4N\mu-1} \times \frac{e^{-2Ns\alpha^2 uv} (H_-(0, iNs\alpha^2))^{\mu} (H_+(0, iNs\alpha^2))^M}{Z_{\underline{m}} \sqrt{1 + 2Ns\,\widetilde{\mathrm{var}}(z)}} \times \exp\left(-\frac{(\tilde{E}(z) - z_0 + \alpha(u-v))^2 Ns}{(1 + 2Ns\,\widetilde{\mathrm{var}}(z))}\right) \quad \text{(A 1.5)}$$

H_-, H_+, $\tilde{E}(z)$ and $\mathrm{var}(z)$ are evaluated using the threshold frequencies appropriate for the shifted optimum, and so depend on u. However, this dependence is weak, because the population is unlikely to lie near the threshold. (As noted above, there is a slight approximation here, because the domain of attraction of the different equilibria does not have the rectangular shape implied by dividing the allele frequency space at fixed thresholds. This approximation is needed, however, to make the integrals separable.)

The chance per generation of a shift from $[m, 0, M]$ to $[m-1, 0, M+1]$ is given by eqn (12) where $\int_S \psi_0\,dS = \tilde{\psi}_0(u)$, and $\epsilon = u$; the integral over u is taken between the two stable equilibria, $u = p$ and $u = P$.

The distribution of the phenotypic mean and variance

The expected variance is (from eqn 14*c*):

$$E(v) = \iiint\int \frac{v e^{-iz\tilde{z}} e^{-iv\tilde{v}} e^{-Ns(z-z_0)^2}}{Z_{\underline{m}}(2\pi)^2} \times (H_-(\alpha\tilde{z}, \alpha^2\tilde{v}))^{\underline{m}} (H_+(\alpha\tilde{z}, \alpha^2\tilde{v}))^M \,d\tilde{z}\,d\tilde{v}\,dz\,dv. \quad \text{(A 1.6)}$$

This is similar to the integral used to derive $Z_{\underline{m}}$ (eqn A 1.1); it differs in that the integral over v gives the

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Fourier transform of $v.\exp(-Nsv)$, which is the differential of a delta function $(i\partial\delta(\tilde{v}-iNs)/\partial\tilde{v})$. If this is integrated by parts:

$$E(v) = \int \frac{e^{-z_0\tilde{z}}e^{-t\tilde{z}^2/4Ns}}{Z_{\underline{m}}\sqrt{(2\pi.2Ns)}} \times\left[-i\frac{\partial}{\partial\tilde{v}}\{(H_-(\alpha\tilde{z}, i\alpha^2Ns))^m(H_+(\alpha\tilde{z}, i\alpha^2N\sigma))^M\}\right]d\tilde{z} \quad \text{(A 1.7)}$$

(where the differential $\partial/\partial\tilde{v}$ is evaluated at $\tilde{v} = iNs$).

Next, apply the 'partial Gaussian' approximation, and expand the term $\partial(H_-^mH_+^M)/\partial\tilde{v}$ as a Taylor series in $\tilde{z}$, as for $Z_{\underline{m}}$. This gives (as before) terms involving $\tilde{E}(pq)$, $\tilde{E}(z)$, and $\widetilde{\text{var}}(z)$, these moments being taken across the distribution $(pq/2)^{4N\mu-1}\exp(-2Ns\alpha^2pq)$ which obtains if fluctuations from the optimum are ignored. There are now also terms $\hat{E}(p-q)$, and $\widehat{\text{var}}(p-q)$, these moments being taken across the distribution $(pq/2)^{4N\mu}\exp(-2Ns\alpha^2pq)$. A little algebra gives:

$$E(v) = 2\alpha^2\left[m\tilde{E}_-(pq)\sqrt{\frac{\nu}{\nu_-}}\exp\left(Ns\left\{\frac{\Delta^2}{2\nu}-\frac{\Delta_-^2}{2\nu_-}\right\}\right) + M\tilde{E}_+(pq)\sqrt{\frac{\nu}{\nu_+}}\exp\left(Ns\left\{\frac{\Delta^2}{2\nu}-\frac{\Delta_+^2}{2\nu_+}\right\}\right)\right] \quad \text{(A 1.8)}$$

where $\nu = 1+2Ns\,\text{var}(z)$ $\quad \Delta = \tilde{E}(z)-z_0$

$$\nu_- = \nu+2Ns\alpha^2(\widehat{\text{var}}_-(p-q)-\widetilde{\text{var}}_-(p-q))$$
$$\Delta_- = \Delta+\alpha(\hat{E}_-(p-q)-\tilde{E}_-(p-q))$$

$$\nu_+ = \nu+2Ns\alpha^2(\widehat{\text{var}}_+(p-q)-\widetilde{\text{var}}_+(p-q))$$
$$\Delta_+ = \Delta+\alpha(\hat{E}_+(p-q)-\tilde{E}_+(p-q)).$$

The mean and variance of z can be found in a similar way:

$$E(z) = z_0+\frac{(\tilde{E}(z)-z_0)}{(1+2Ns.\widetilde{\text{var}}(z))} \quad \text{(A 1.9)}$$

$$\text{var}(z) = \frac{\widetilde{\text{var}}(z)}{(1+2Ns.\widetilde{\text{var}}(z))}. \quad \text{(A 1.10)}$$

When $2Ns.\widetilde{\text{var}}(z)$ is large, the expected mean approaches the optimum, and the variance of fluctuations in the mean approaches $1/2Ns$. These are just the values expected from naive phenotypic arguments (eqn 8). At the other extreme, when $2Ns.\text{var}(z)$ is small, the mean and variance of z approach the values $\tilde{E}(z)$, $\widetilde{\text{var}}(z)$ which are expected when there is no directional force pushing z towards the optimum.

It is not easy to guess the size of the crucial parameter $2Ns.\widetilde{\text{var}}(z)$: as population size increases, $\text{var}(z)$ decreases. If allele frequencies are usually close to fixation, the integral

$$\int(pq/2)^{4N\mu-1}\exp(-2Ns\alpha^2pq)\,dp$$

is approximately

$$\int(p/2)^{4N\mu-1}\exp(-2Ns\alpha^2p)\,dp,$$

and so $\widetilde{\text{var}}(p)\approx\mu/(Ns\alpha^2)^2$, and $2Ns.\widetilde{\text{var}}(z)\approx 8n\mu/s\alpha^2$. We have assumed that n is large and that $\mu/s\alpha^2$ is small; however, $8n\mu/s\alpha^2$ could be large or small. These arguments suggest that the phenotypic arguments used to derive eqn (8) will only be valid if there are very large number of loci, and if allele frequencies at each locus are not too low. We can see these conditions from a different angle by noting that $2Ns.\widetilde{\text{var}}(z) = 8n\mu/s\alpha^2 = 2V^*/\alpha^2$, the ratio between V^*, the equilibrium variance under the rare alleles approximation, and the variance of a single substitution: the phenotypic arguments will hold when α^2 is much smaller than the total standing genetic variance.

Appendix 2. Details of the full Gaussian approximation

The distribution of the mean and variance

The distribution of the mean and variance, for populations near to some equilibrium $\underline{m}$, is $\psi_0(z,v) = W(z,v)^{2N}F_{\underline{m}}(z,v)/Z_{\underline{m}}$ (eqn 13), where $F_{\underline{m}}(z,v)$ is given by eqn (14). For Gaussian stabilizing selection on a large number of loci, this distribution is itself almost exactly Gaussian, and so can be summarized by its mean and variance.

Exact integration cannot give explicit analytic results. By making the strong assumption that the allele frequencies are normally distributed (the 'Gaussian approximation'), some analytic results can be obtained from the distribution of average allele frequencies, $\tilde{\psi}_0(p,P)$ (eqn 18). Since $\tilde{\psi}_0(p,P)$ is sharply peaked, it can be approximated by a Gaussian with the same curvature (Fig. 2*b*). Hence, the variance of p and P is given by the inverse of the matrix of second differentials of $\tilde{\psi}_0$. This curvature matrix is proportional to the matrix of second derivatives of U (eqn 4*a*). The phenotypic mean and variance are related to the average allele frequencies; from eqn (2):

$$z = \alpha[m(p-q)+M(P-Q)] \quad \text{(A 2.1}a\text{)}$$

$$v = 2\alpha^2\left[mpq+MPQ-\sum_{i=1}^{m}(p_i-p)^2-\sum_{i=m+1}^{n}(p_i-P)^2\right]. \quad \text{(A 2.1}b\text{)}$$

We see that the expectation of z is equal to its value at the peak of $\tilde{\psi}_0$. However, the expected phenotypic variance is reduced first, by fluctuations around the averages at individual loci, and second, by fluctuations in the averages themselves.

These considerations lead to complicated and obscure expressions. However, if the mean of the deterministic equilibrium coincides with the optimum,

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we can write $pq = PQ = \mu/s\alpha^2 \equiv \gamma$, and these expressions simplify considerably:

$$E(v) = (4n\mu/s)\left(1 - \frac{(1+8\gamma(n-2))}{2Ns\alpha^2(1-8\gamma)(1+8\gamma(n-1))}\right) \quad \text{(A 2.2}a\text{)}$$

$$\text{var}(z) = \frac{(4n\mu/s)}{Ns\alpha^2(1+8\gamma(n-1))} \quad \text{(A 2.2}b\text{)}$$

$$\text{var}(v) = \frac{(4n\mu/s)(1-8\gamma+16mM\gamma/n)}{(Ns(1+8\gamma(n-1)))} \quad \text{(A 2.2}c\text{)}$$

where $\gamma = \mu/s\alpha^2$.

These values can be compared with the phenotypic approximations of eqn (8). Suppose that n is large, and $\gamma = \mu/s\alpha^2$ is small. Then, eqn (A 2.2a) predicts that sampling drift will decrease the phenotypic variance, v, by a factor $(1/2Ns\alpha^2)$. This conflicts with the prediction of a factor $(1/Ns\alpha^2)$, from eqn (8). Simulations show that in fact, neither method is particularly accurate (Fig. 8, and below).

The predicted variances of z and v differ from the phenotypic predictions by factors involving $n\gamma$. For the range of parameters considered here, this could be large or small: the variance of z agrees with eqn (8) when $n\gamma$ is large, whilst the variance of v agrees when $n\gamma$ is small. The discrepancy arises through the accumulation of small deviations (of order γ) from the assumptions of eqn (8) at many (n) loci.

The distribution across equilibria

The probability that a population will be found near some particular equilibrium in the class $[m, 0, M]$ can be found by integrating $\tilde{\psi}_0(p, P)$. Since this distribution is approximately Gaussian, the integral introduces a factor $\sqrt{\det(2\pi/\log(\tilde{\psi}_0)'')}$, where $\log(\tilde{\psi}_0)''$ is the curvature matrix. This curvature matrix can be found directly by exact integration. With the Gaussian approximation, an explicit formula can be found: multiplying eqn (18) by this factor:

$$\frac{Z_m}{Z} = \frac{\exp(2NU)}{Z}\sqrt{\left(\frac{2\pi}{Ns\alpha^2}\right)^n \frac{1}{D}} \quad \text{(A 2.3)}$$

D is the product of eigenvalues of the deterministic equations (eqn 4a); this expression could of course be obtained directly from that determinant, without passing through the intermediate calculation of $\tilde{\psi}_0(p, P)$. The probability of being near a particular equilibrium depends mainly on the potential U, but also decreases with D: equilibria which are extremely stable, in the sense of having large D, are surrounded by a more compact cloud of populations.

Transitions between equilibria

Consider a shift from somewhere near one equilibrium in the class $[m, 0, M]$, via the unstable state $[m, 1, M-1]$, towards a new state, $[m+1, 0, M]$. Label the initial stable state S, and the unstable intermediate U. The probability that such a shift will occur is Γ per unit time; conversely, the expected time before a shift is Γ^{-1}. The transition rate is given by eqn (12). We must make the slight approximation that the ridge of probability which connects the two stable states represents change of allele frequency at one locus (p_i, say). Integration across transverse surfaces S then requires that ψ_0 be integrated over the other $n-1$ allele frequencies, keeping p_i fixed. This gives the marginal distribution of p_i, which will have a minimum at the unstable threshold, ρ. The integral of the inverse of this marginal distribution gives the inverse of the transition rate (eqn 12). Note that fluctuations at all the loci will affect the marginal distribution of p_i, and so this method gives different (and better) results than the simple single-locus approximations discussed above.

If we assume that the allele frequency distribution ψ_0 is Gaussian, transition rates are simply given by eqn (15) of Barton & Rouhani (1987):

$$\Gamma = \frac{\lambda}{2\pi}\sqrt{\frac{V_U D_S}{-V_S D_U}}\exp(-2N\Delta U) \quad \text{(A 2.4)}$$

D_S, D_U are the determinants which give the stability of the system near the stable and unstable points (eqn 4), and V_S, V_U are the products of the genetic variances (eqn 5) at these points. λ is the leading eigenvalue at the unstable point.

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