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# Fluctuating environments and the role of mutation in maintaining quantitative genetic variation

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**Summary**

We study a class of genetic models in which a quantitative trait determined by several additive loci is subject to temporally fluctuating selection. Selection on the trait is assumed to be stabilizing but with an optimum that varies periodically and might be perturbed stochastically. The population mates at random, is infinitely large and has discrete generations. We pursue a statistical and numerical approach, covering a wide range of ecological and genetic parameters, to determine the potential of fluctuating environments to maintain quantitative genetic variation. Whereas, in contrast to some recent claims, this potential seems to be rather limited in the absence of recurrent mutation, fluctuating environments might, in combination with it, often generate high levels of additive genetic variation. We investigate how the genetic variation maintained depends on the ecological parameters and on the underlying genetics.

## 1. Introduction

Populations inhabit environments that are not uniform but that might be structured and variable in time or space. Most individuals within a local subpopulation will experience similar environmental conditions that change on time scales shorter than a generation and within the range of movement of individuals. However, there is also temporal variation on time scales longer than one generation and variation between different patches of habitat. Such macro-environmental variation might have a profound influence on the genetic composition of a population by inflicting changing selective pressures that will promote evolutionary response. In this article, we investigate some of the evolutionary consequences of environments that fluctuate between generations. The causes of such fluctuations might range from changes in the abiotic environment to variation in the density of other, ecologically relevant, species, but they enter the model only indirectly through the shape and time dependence of the assumed fitness function.

It has long been known that 'a mere series of changes in the direction of selection may be enough to secure polymorphism' (Haldane & Jayakar, 1963) but the extent to which temporarily varying selection can maintain genetic variation in a population seems to be largely unknown. Quantitatively, this problem seems not to be settled even for a single diallelic locus. If selection changes periodically then a simple sufficient condition for the maintenance of a protected polymorphism (typically not an equilibrium but a periodic solution) at a single diallelic locus is that the geometric mean fitness of both homozygotes (averaged over a full selection cycle) will be lower than the corresponding fitness of the heterozygote. Such conditions have been found for complete dominance (Haldane & Jayakar, 1963; Hoekstra, 1975; see Appendix i for a brief summary). A complete characterization of the limiting behaviour has been obtained only for very simple models of cyclical selection (e.g. Karlin & Liberman, 1974; Nagylaki, 1975). In general, diallelic one-locus systems under cyclical selection can show multiple stable (periodic) equilibria (see Appendix iii). Kirzhner *et al.* (1995) showed that so-called supercycles can exist in one-locus models with four alleles and cyclical selection of period two (i.e. cycles with a period much (hundreds of times) longer than the selection cycle). Hence, even in one-locus systems, there is little hope for establishing

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general estimates of the genetic variance that can be maintained under periodic selection.

Sufficient conditions for a protected polymorphism have also been derived for an arbitrary deterministic sequence of selection coefficients. They are related to overdominance in terms of certain 'gliding' geometric averages of fitnesses, but the situation is delicate (Cornette, 1981; Nagylaki, 1992 (pp. 65–71)). Roughly speaking, the single-locus results show that some form of overdominance in the geometric averages (over appropriate time spans) of fitnesses will often ensure the maintenance of genetic variation, or one or the other allele might be fixed, but this can be a very slow process (Hoekstra, 1975).

In a series of papers, Kirzhner and colleagues investigated the possibility of maintaining genetic polymorphism in multilocus models under cyclical selection. They derived general conditions for the stability of polymorphisms in two-locus models of cyclical selection (Kirzhner *et al*., 1996). For instance, a globally stable polymorphism is only possible if the geometric mean fitnesses (averaged over a full selection cycle) of the double homozygotes are lower than the geometric mean fitnesses of the respective single heterozygotes and of the double heterozygotes. However, locally stable polymorphisms are possible even if all double homozygotes have higher geometric mean fitnesses than all other genotypes. Most interestingly, they found that simple periodic changes can lead to extremely complex dynamic behaviour of the gamete frequencies, such as chaos-like attractors or supercycles. Such complex limiting behaviour was shown to occur in two-locus models of strong cyclical selection with very short periods, such as only two seasons (e.g. Kirzhner *et al*., 1995), and in quantitative genetic models in which the trait is determined by two (Korol *et al*., 1996) to six (Kirzhner *et al*., 1996, 1998) loci and is under stabilizing selection with a periodically moving optimum. Kirzhner and colleagues promoted the hypothesis that cyclic environmental change might be an important factor in maintaining genetic polymorphism (Korol *et al*., 1996; Kirzhner *et al*., 1998). They also showed that non-additive gene interaction might relax the conditions needed for protected polymorphisms (Kirzhner *et al*., 1998). For brief summaries of empirical studies of cyclical and fluctuating selection, refer to Korol *et al*. (1996) and Kondrashov & Yampolsky (1996*a*). In this empirical literature, there are indications (but little conclusive evidence) of an association between the temporal environmental heterogeneity and the amount of genetic variation. One of the reasons for this lack of evidence might be the difficulties encountered in measuring (temporally varying) selection.

Because the selection cycles in the investigations of Kirzhner and colleagues are typically very short (two to four generations), their results seem to contradict the results of Kondrashov & Yampolsky (1996*a*) and Bürger (1999) for a very similar model. These authors found that, with a periodically moving optimum, high levels of genetic variation can be maintained, but only if the period is long (at least 20–50 generations) and the amplitude is larger than the width of the fitness function. For periods of 20 generations or fewer, neither Kondrashov & Yampolsky (1996a) nor Bürger (1999) found a detectable increase in genetic variation. This work differs from that of Kirzhner and colleagues in as far as in the model population sizes are finite, many loci contribute to the trait (between 16 and 100), recurrent mutation occurs, stabilizing selection is not as strong and amplitudes are generally smaller. The extent to which the high levels of genetic variation maintained in the models of Kondrashov and Yampolski, and of Bürger depend on the presence of recurrent mutation has not been investigated.

Random temporal variation in fitness has also been studied. For a single diallelic locus, Karlin & Liberman (1974) derived conditions under which fixation of an allele almost never occurs, or under which fixation is a stochastically locally stable phenomenon (i.e. one that occurs with high probability if the allele is rare). These are related to the above mentioned conditions: for instance, fixation of an allele almost never occurs if the expected logarithmic fitnesses of its homozygotes are lower than the corresponding fitnesses of the heterozygotes. However, biologically, this condition is not sufficient to ensure a protected polymorphism because the allele can temporarily become so rare that it will be lost in a finite population; for similar phenomena in non-periodic deterministic sequences of selection coefficients, see Cornette (1981) and Nagylaki (1992). A comprehensive treatment of a class of models with randomly fluctuating fitnesses that can be analysed by means of diffusion approximation can be found in Gillespie (1991). Although these models are designed to study molecular evolution, they share much with some standard quantitative-genetic models. In summary, with stochastically fluctuating fitnesses, genetic variation can be maintained in situations in which this would be impossible for constant fitnesses that coincide with the respective expectations; in particular models, much variation can be maintained.

For quantitative-genetic models in which the position of the optimum fluctuates randomly across generations without autocorrelation (e.g. so that the position of the optimum in each generation is drawn from a normal distribution), no or little increase of variance occurs relative to mutation-stabilizing selection balance with a resting optimum. This has been shown on the basis of various approximations (Lande, 1977; Turelli, 1988) and by computer simulations (Bürger, 1999). However, in such models, maintenance of genetic variation is not impossible in the absence of

mutation (Gillespie & Turelli, 1989; see also Zonta & Jayakar, 1988, for a special two-locus model). If the position of the optimum changes with positive serial correlation then the mean fitness of a population can be increased by an increasing genetic variance, suggesting that this kind of temporal variation in fitness has the potential to increase genetic variation, provided that the genetic system is flexible enough (Slatkin & Lande, 1976; Charlesworth, 1993; Lande & Shannon, 1996). All these studies assume discrete, nonoverlapping generations. For a model of an age-structured population with discrete (overlapping) generations, Ellner (1996) showed that fluctuating selection *per se* can maintain genetic variation if the variance of the fluctuations is sufficiently large. In his model, individuals in different age classes might have been exposed to different selective pressures because selection acts only on newborns. Also, the number of individuals in each stage is constant with density-dependent recruitment, implying a kind of soft selection.

In this article, we explore the potential of fluctuating selection to maintain genetic variation in quantitative traits in the absence and presence of recurrent mutation. The diploid population has discrete non-overlapping generations, is infinitely large and mates randomly. The trait is under stabilizing selection with an optimum that changes periodically, with or without random distortions, and is determined by up to six diallelic loci. For a given set of 'ecological' parameters (strength of stabilizing selection, period and amplitude of the cycle, amount of stochasticity), a given number of loci and a given mutation rate, the recursion relations are iterated for many randomly chosen sets of genetic parameters (allelic effects and recombination rates) until stationarity is reached. The quantities of interest are then measured. In this way, the average asymptotic geometric mean fitness, the average asymptotic genetic variance and so on are obtained for each set of parameters. In the absence of mutation, we find that almost any such fluctuating selection reduces the genetic variance of a trait relative to that under a resting optimum. Recurrent mutation, however, even if very weak, can radically alter this and lead to several interesting phenomena.

## 2. General model

We consider a quantitative character that is controlled additively by $n$ diallelic loci in an infinite, randomly mating diploid population. The contribution of one allele at each locus $l$ is 0, and the contribution of the other allele ($\beta_l$) is a random number between 0 and 1. We assume that the minimum and maximum genotypic values are always 0 and 1, respectively. Therefore, the actual contribution by the second allele at locus $l$ ($\alpha_l$) is scaled to be $0{\cdot}5\,\beta_l/\Sigma_{k=1}^{n}\beta_k$. This implies that the genotypic value of the total heterozygote is always 0·5 and that the average allelic effect among the $n$ loci controlling the trait is $\bar{\alpha} = 1/2n$. This normalization has the advantage that the strength of selection on genotypes can be compared for different numbers of contributing loci. Environmental variance is ignored, so that genotypic values and phenotypic values are identical. In the absence of genotype–environment interaction, this is no restriction because, in the present model, the only effect of including environmental variance was a reduction in the selection intensity.

The trait is under Gaussian stabilizing selection, with the optimum genotype $\theta_t$ exhibiting temporal change; that is, the viability of an individual with genotype $G$ is assumed to be

$$W_{G,t} = \exp[-s(G-\theta_t)^2], \tag{1}$$

where $s$ measures the strength of stabilizing selection and is independent of the generation number $t$. Selection acts only through different viabilities. The position of the optimum is assumed to fluctuate periodically about the midpoint of the range of genotypic values (0·5); in addition, its position can be randomly perturbed. More precisely, we assume that $\theta_t$ is drawn from a normal distribution with mean

$$\theta_t = 0{\cdot}5 + A\sin(2\pi t/L), \tag{2}$$

(where $A$ is the amplitude and $L$ the period of the selection cycle) and standard deviation

$$\sigma_\theta = dA, \tag{3}$$

where $d$ is a measure of the magnitude of stochasticity. If $d = 0$, there is purely periodic selection; if, in addition, $A = 0$, there is pure Gaussian stabilizing selection. The reason that the 'noise term' (Eqn 3) is scaled with the amplitude is that we are mainly interested in small deviations from periodic selection, and a fixed standard deviation would perturb cycles with small amplitudes more than cycles with large amplitudes. Fig. 1 shows the effects of random perturbations on the position of the optimum.

Gametes are designated by $i$, their frequencies among zygotes in consecutive generations by $p_i$ and $p_i'$, and the fitness of a zygote consisting of gametes $j$ and $k$ by $W_{jk}$ (omitting the time dependence). Let $R(j, k \to i)$ denote the probability that a randomly chosen gamete produced by a $jk$ individual is $i$. The function $R$ is determined by the pattern of recombination between loci. At each locus, recurrent mutation occurs at rate $u$ per gamete and generation; that is, all genes have the same mutation rate $u$. It is then straightforward to calculate the mutation rate $u_{ij}$ from gamete $i$ to gamete $j$. With these ingredients, the system of recursion relations describing the dynamics

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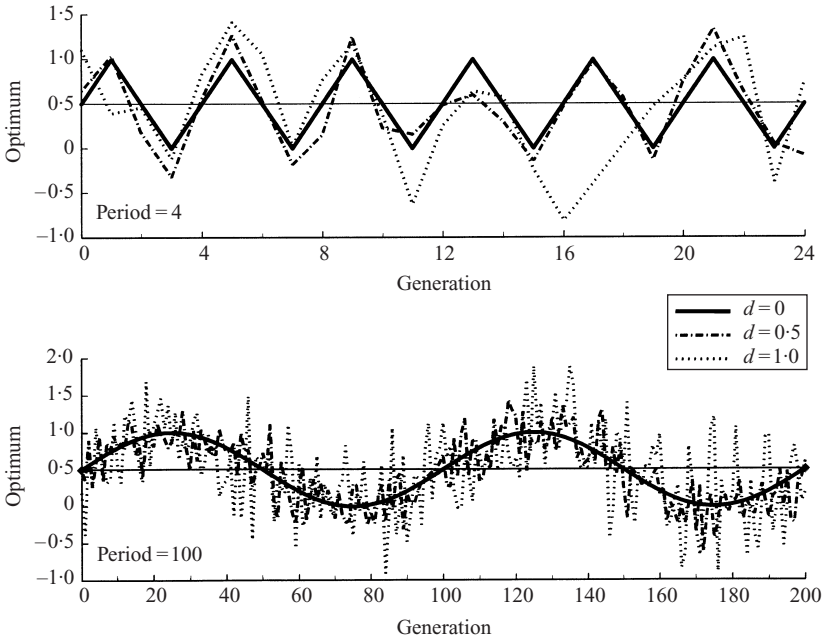


Fig. 1. The movement of a cyclically fluctuating optimum without and with random perturbations according to Eqns 2 and 3. The amplitude is $A = 0{\cdot}5$ in both cases, the upper panel is for a period of $L = 4$, the lower for $L = 100$. The results of different values of the parameter $d$ (which measures the amount of stochasticity) are as in Fig. 6; if $d = 0$, the optimum is purely periodic and, if $d = 1$, there are substantial random perturbations of its deterministic position.

of the distribution of gametes under viability selection followed by recombination and mutation is given by

$$p_i' = p_i^* + \Sigma_{j:j\neq i} p_j^* u_{ji} - p_i^* u_{ij}, \tag{4a}$$

where

$$p_i^* = \bar{W}^{-1}\Sigma_{j,k} W_{jk} p_j p_k R(j, k \to i) \tag{4b}$$

denotes the frequency of gamete $i$ after selection and recombination, and $\bar{W}^{-1}\Sigma_{j,k} W_{jk} p_j p_k$ is the mean fitness (e.g. Bürger, 2000).

With cyclical selection of period $L$, an equilibrium is typically periodic with period $L$; that is, it satisfies $p_i(\tau + L) = p_i(\tau)$ for $\tau = 1, \ldots, L$ and every $i$.

## 3. Statistical approach

Usually, the parameters of genetic systems that control quantitative traits are unknown or can be inferred only indirectly. Because, in addition, the dimensionality of the parameter space and the space of gamete frequencies increases rapidly as the number of loci increases, an explicit and analytical characterization of the equilibrium properties of multilocus models in terms of all parameters and initial conditions would be of limited value, even if it were feasible. Therefore, we have used the different approach of evaluating the quantities of interest for randomly chosen parameter sets and initial conditions, consequently obtaining statistical results.

We proceeded as follows. For a given set of ecological parameters (strength $s$ of stabilizing selection, selection-cycle amplitude $A$ and period $L$, and amount $d$ of stochasticity in the position of the optimum), a given number $n$ of loci and a given per-locus mutation rate $u$, we constructed 1000–4000 'genetic parameter sets' (the allelic effects of loci and recombination rates between adjacent loci). For each genetic parameter set, allelic effects were obtained by generating values $\beta_l$ ($l = 1, 2, \ldots, n$) as independent random variables, uniformly distributed between 0 and 1, and transforming them into the actual allelic effects $\alpha_l = 0{\cdot}5\beta_l/\Sigma_k \beta_k$. The additivity assumption yields the genotypic values and, from Eqns 1–3, the genotypic fitnesses $W_{jk}$ are calculated in each generation. Recombination rates between adjacent loci, $r_{l,l+1}$ ($l = 1, \ldots, n-1$), were obtained as independent random variables, uniformly distributed between 0 and 0·5. Because this yields a high average recombination rate and because the influence of recombination is of interest, we also performed iterations in which the recombination rates between adjacent loci were fixed (and small), so that only allelic effects were chosen randomly. In all cases we assumed that there was no interference.

For each of such constructed genetic parameter sets, the recursion relations (Eqn 4) were numerically iterated starting from a single random initial distribution of gametes. In the absence of stochasticity ($d = 0$), an iteration was stopped after generation $t$ when either a (periodic) equilibrium was reached (in the sense that the geometric distance between gametic distributions at the end of two consecutive selection

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cycles $[\Sigma_i|p_i(t+L)-p_i(t)|^2]^{0.5}$, with $t$ a multiple of $L$, is $< 10^{-12}$) or $t$ exceeded 300000 generations. In the latter case, no equilibrium was reached. Usually, the proportion of such runs was very small; their statistical treatment is described further below. There are two reasons why convergence does not occur within 300000 generations: (1) slow convergence; or (2) no periodic solution is approached. Inspection of the output showed that, in most cases, slow convergence was the likely reason why an iteration exceeded 300000 generations. However, in some cases, the trajectories indeed showed complex dynamic behaviour, similar to what Kirzhner and colleagues observed (see the Introduction).

From the raw data of each parameter set (i.e. the gamete frequencies in every generation of the final selection cycle), we calculated the following quantities by averaging over this last selection cycle: arithmetic average of the mean genotypic values, arithmetic average $\bar{V}$ of the genetic variances, arithmetic average $\bar{V}_r$ of the ratios $V/V_{\max}$ of the genetic variance and the maximum possible variance in the given genetic system under linkage equilibrium ($V_{\max}$), and the geometric average $\bar{W}_g$ of population mean fitness. The number of polymorphic loci was also recorded. These values were then averaged over all genetic parameter sets and standard deviations were calculated. This yielded our quantities of interest for each set of ecological parameters, number of loci and mutation rates. We refer to $\bar{V}_r$ as the relative genetic variance. Its use is preferable when comparing systems with different number of loci, because the variance itself is strongly dependent on the average effect across loci, which decreases according to $1/(2n)$. For a given number of loci, the relative genetic variance $\bar{V}_r$ and the real (average) genetic variance $\bar{V}$ behave very similarly (results not shown). Because $V_{\max} = 0{\cdot}5\Sigma_i\alpha_i^2$, the expectation (and, in principle, the whole distribution) of $V_{\max}$ can be calculated for each $n$. For instance, if $n = 4$, we have $E[V_{\max}] = 0{\cdot}25(1-44\ln 2+27\ln 3) \approx 0{\cdot}041$. For $n = 2$ and $n = 6$, the numerical values are 0·077 and 0·028, respectively. Multiplying $\bar{V}_r$ by $E[V_{\max}]$ yields an estimate of $\bar{V}_r$ that is typically smaller than, but almost always within about 20% of, the 'true' value (results not shown). The arithmetic average of mean fitness was also recorded but the results are not shown because, from the theory reviewed in the Introduction and the Appendix, it follows that the geometric average is more informative.

Iterations that did not reach equilibrium within 300000 generations, subsequently called slow runs, had no apparent trend in deviating from convergent runs. Therefore, slow runs were included in these statistics. Only for calculating (in the absence of mutation) the proportion of runs converging to a (periodic) equilibrium involving a given number of polymorphic loci were the slow runs excluded, for obvious reasons. For the computations with a stochastically perturbed optimum ($d > 0$), we pursued a slightly different procedure because no deterministic equilibrium is approached (except when a population ends up in a completely monomorphic state). To obtain estimates of our quantities of interest, we stopped the iterations after 50000 generations and averaged all quantities of interest over the final ten selection cycles. Comparison with additional computations for some selected parameter sets over 300000 or 500000 generations showed that the longer computations yielded statistically significant differences only in the absence of mutation. This will be discussed further below.

## 4. Periodic environments

We first consider a trait determined by four loci and describe how the asymptotic properties of the evolving population depend on the amplitude and period of the selection cycle if there is no mutation. Then, we study the role of mutation. For this 'basic data set', obtained from all combinations of chosen values of $A$, $L$ and $u$, the strength of stabilizing selection is fixed and relatively high. Afterwards, we investigate the effects of weaker stabilizing selection and of linkage for a subset of this parameter set. Finally, we explore how our findings depend on the number of loci by presenting results for two and six loci. The influence of random perturbations of the environment is studied in the next section.

### (i) *Basic data set*

For this basic data set, we consider a trait determined by four loci and assume stabilizing selection of (fixed) strength $s = 5$. This is relatively strong selection and means that if the optimum is in the middle of the range of possible genotypic values, the fitness of the most extreme genotypes is $\exp(-1{\cdot}25) \approx 0{\cdot}287$. For every combination of the parameters $L = 1$, 4, 8, 24, 52, 100 and 200, $A = 0{\cdot}25$, 0·5 and 1, and $u = 0$, $5\times10^{-6}$, $5\times10^{-5}$ and $5\times10^{-4}$, 4000 genetic parameter sets were generated by the procedure described in the previous section. In particular, recombination rates between adjacent loci are uniformly distributed between 0 and 0·5. The recursion relations were iterated and the quantities of interest measured as described above. We note that $L = 1$ implies that there is pure stabilizing selection because the optimum is constant, and $A = 0{\cdot}5$ means that the optimum cycles between the most extreme genotypes; thus, there is always a genotype that is close to the optimum. It is only for $A = 1$ that there are periods of pure directional selection, namely when the optimum is outside the

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Table 1. *Equilibrium structure under periodic selection in the absence of mutation. The percentages of (stable) equilibria with the given number of polymorphic loci in a four-locus system are listed without mutation and with* s = 5. *Because four polymorphic loci were never observed, the corresponding column has been omitted. Each entry is based on 4000 genetic parameter sets, but slow runs are excluded from these statistics. An entry of 0·00 indicates that the corresponding frequency is less than 0·005, and – indicates that this outcome was never observed*

| Environmental variables | | Polymorphic loci | | | | |
|---|---|---|---|---|---|---|
| Amplitude | Period | 0 | 1 | 2 | 3 | Slow runs |
| 0 | 1 | 0·60 | 0·39 | 0·01 | 0·00 | 34 |
| 0·25 | 4 | 0·60 | 0·39 | 0·01 | 0·00 | 33 |
| 0·25 | 8 | 0·60 | 0·38 | 0·01 | 0·00 | 34 |
| 0·25 | 24 | 0·61 | 0·38 | 0·01 | 0·00 | 43 |
| 0·25 | 52 | 0·61 | 0·38 | 0·01 | 0·00 | 48 |
| 0·25 | 100 | 0·57 | 0·42 | 0·01 | 0·00 | 35 |
| 0·25 | 200 | 0·66 | 0·33 | 0·01 | 0·00 | 37 |
| 0·5 | 4 | 0·59 | 0·39 | 0·02 | 0·00 | 33 |
| 0·5 | 8 | 0·61 | 0·38 | 0·02 | 0·00 | 35 |
| 0·5 | 24 | 0·57 | 0·42 | 0·01 | 0·00 | 43 |
| 0·5 | 52 | 0·57 | 0·42 | 0·01 | 0·00 | 40 |
| 0·5 | 100 | 0·67 | 0·32 | 0·01 | 0·00 | 38 |
| 0·5 | 200 | 0·78 | 0·22 | 0·00 | – | 41 |
| 1·0 | 4 | 0·60 | 0·39 | 0·01 | – | 42 |
| 1·0 | 8 | 0·58 | 0·41 | 0·01 | 0·00 | 31 |
| 1·0 | 24 | 0·55 | 0·44 | 0·01 | 0·00 | 45 |
| 1·0 | 52 | 0·67 | 0·32 | 0·01 | 0·00 | 43 |
| 1·0 | 100 | 0·78 | 0·22 | 0·00 | – | 42 |
| 1·0 | 200 | 0·90 | 0·10 | 0·00 | – | 38 |

Table 2. *Effect of mutation on the relative genetic variance* $\bar{V}_r$ *for four-locus systems with* s = 5 *and the indicated amplitudes A and periods L. Column 3 displays the arithmetic average,* $\bar{V}_r$ *of* $V/V_{max}$ *in the absence of mutation, columns 4–6 display the ratio of the relative variance with mutation (as indicated) to that without mutation, and the last four columns give the standard deviations of* $\bar{V}_r$ *for the indicated mutation rates in multiples of* $\bar{V}_r$

| Environment | | | $\bar{V}_r(\mu)/\bar{V}_r(\mu=0)$ | | | Standard deviation of $V_r(\mu)$ | | | |
|---|---|---|---|---|---|---|---|---|---|
| $A$ | $L$ | $\bar{V}_r(\mu=0)$ | $5\times10^{-6}$ | $5\times10^{-5}$ | $5\times10^{-4}$ | $\mu=0$ | $5\times10^{-6}$ | $5\times10^{-5}$ | $5\times10^{-4}$ |
| 0 | 1 | 0·046 | 1·0 | 1·0 | 1·4 | 2·2 | 2·3 | 2·1 | 1·4 |
| 0·25 | 4 | 0·044 | 1·1 | 1·1 | 1·6 | 2·3 | 2·2 | 2·1 | 1·4 |
| 0·25 | 8 | 0·044 | 1·0 | 1·1 | 1·6 | 2·2 | 2·2 | 2·0 | 1·3 |
| 0·25 | 24 | 0·039 | 1·0 | 1·2 | 2·3 | 2·0 | 2·0 | 1·7 | 0·9 |
| 0·25 | 52 | 0·031 | 1·3 | 2·2 | 5·7 | 1·9 | 1·6 | 1·0 | 0·3 |
| 0·25 | 100 | 0·024 | 4·0 | 6·8 | 10·8 | 1·9 | 0·6 | 0·3 | 0·1 |
| 0·25 | 200 | 0·018 | 8·9 | 11·4 | 15·0 | 2·1 | 0·4 | 0·3 | 0·2 |
| 0·5 | 4 | 0·045 | 0·9 | 1·0 | 1·6 | 2·2 | 2·1 | 1·9 | 1·3 |
| 0·5 | 8 | 0·040 | 1·0 | 1·1 | 1·9 | 2·1 | 2·0 | 1·8 | 1·0 |
| 0·5 | 24 | 0·035 | 1·3 | 2·5 | 7·5 | 1·7 | 1·4 | 0·7 | 0·1 |
| 0·5 | 52 | 0·024 | 7·3 | 9·7 | 13·1 | 1·6 | 0·2 | 0·2 | 0·2 |
| 0·5 | 100 | 0·016 | 10·8 | 13·0 | 17·7 | 1·6 | 0·2 | 0·2 | 0·1 |
| 0·5 | 200 | 0·011 | 15·6 | 19·8 | 27·0 | 1·7 | 0·2 | 0·2 | 0·1 |
| 1·0 | 4 | 0·042 | 1·0 | 1·0 | 1·9 | 2·0 | 2·0 | 1·8 | 1·0 |
| 1·0 | 8 | 0·036 | 1·1 | 1·5 | 4·3 | 1·8 | 1·7 | 1·2 | 0·4 |
| 1·0 | 24 | 0·026 | 7·0 | 8·9 | 10·6 | 1·5 | 0·2 | 0·2 | 0·2 |
| 1·0 | 52 | 0·014 | 9·3 | 10·4 | 12·2 | 1·6 | 0·2 | 0·1 | 0·1 |
| 1·0 | 100 | 0·010 | 9·6 | 11·0 | 13·7 | 1·6 | 0·1 | 0·1 | 0·1 |
| 1·0 | 200 | 0·008 | 9·8 | 11·7 | 15·3 | 1·7 | 0·1 | 0·1 | 0·1 |

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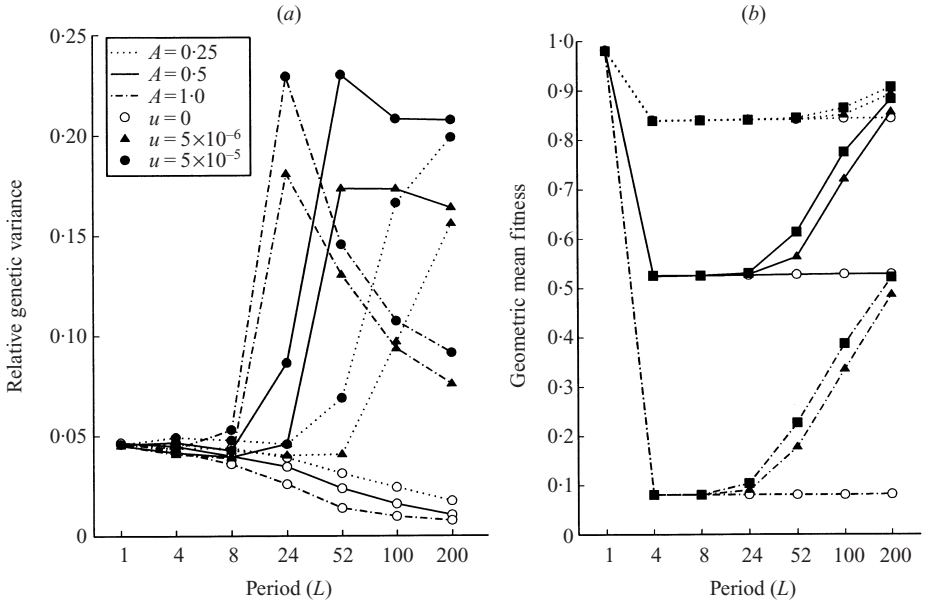


Fig. 2. (*a*) Displays the relative genetic variance $\bar{V}_r$ (i.e. the arithmetic average of $V/V_{\max}$) for all combinations of the three indicated mutation rates and the three amplitudes as a function of the period of the selection cycle. (*b*) The corresponding curves for the geometric average of mean fitness $\bar{W}_g$. The strength of stabilizing selection is $s = 5$ in all cases, and the position of the optimum is purely periodic ($d = 0$).

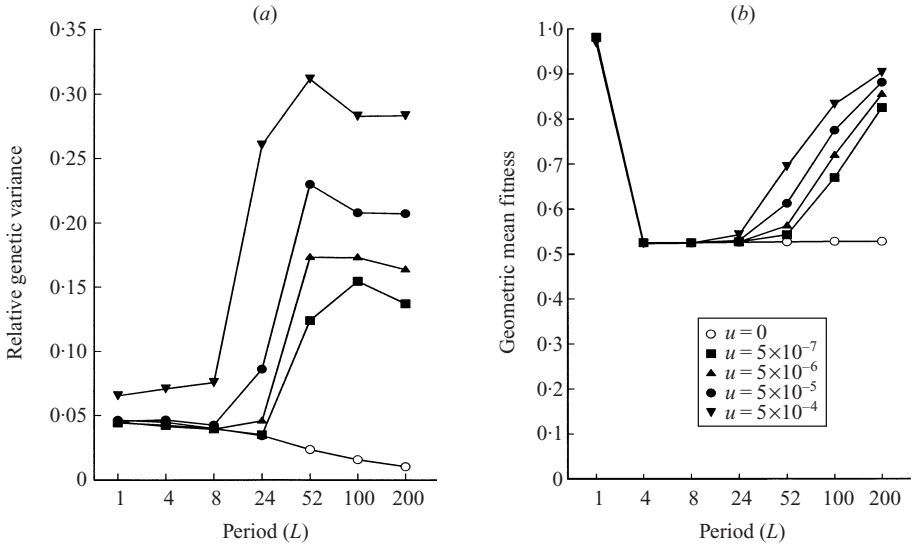


Fig. 3. As for Fig. 2 but the effect of mutation is shown for a much larger range of mutation rates. $A = 0{\cdot}5$, $s = 5$ and $d = 0$.

range of possible genotypic values. The main results are summarized in Tables 1, 2 and in Figs. 2, 3.

(ii) *No mutation*

Table 1 shows that, in the absence of mutation and nearly independently of the amplitude, fixation of all loci occurs in $\sim 60\,\%$ of all (4000) genetic parameter sets if the period is short or intermediate, or if the environment is constant. In a few cases, selection with intermediate period does lead to a slightly higher frequency of polymorphisms, but the effect is hardly significant. For sufficiently long periods, the proportion of polymorphic loci decreases substantially. The larger the amplitude, the more pronounced is the loss of polymorphism and the lower the period at which this decay begins. For every parameter combination ($L$, $A$, $u$), the frequency of genetic parameter sets maintaining two or more loci polymorphic is $< 2\,\%$, the frequency of parameter sets maintaining three loci polymorphic is $< 0{\cdot}3\,\%$ and in no instance was a four-locus polymorphism observed. Thus the

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most likely event is that all loci go to fixation; otherwise, in almost all cases, a single locus remains polymorphic.

As Table 2 and Fig. 2*a* show, in the absence of mutation, the relative genetic variance decreases monotonically with increasing length of the period. For all parameter sets of Table 2 with $u = 0$, the relative genetic variance under a periodic optimum is lower than under a constant optimum, though for short periods ($L = 4$ or 8) the difference is statistically not significant. With long periods and intermediate or large amplitudes, a substantial decrease in the average variance is observed.

As mentioned in the previous section, there were slow runs in which the iterations did not equilibrate within 300000 generations. In the absence of mutation, their fraction was about 1% (Table 1). In some of these slow runs, apparently complex limiting behaviour was observed, mostly for intermediate periods. Even though they maintain more polymorphism than the convergent runs (usually three or four loci are polymorphic), the maintained genetic variance is well within the range of variances observed for convergent runs. In contrast to the conclusions of Kirzhner *et al.* (1996, 1998), our results suggest that complex limiting behaviour occurs at a non-negligible frequency only in carefully selected regions of the parameter space, at least if loci are additive and selection is not extremely strong.

Interestingly, without mutation, the geometric average of mean fitness is nearly independent of the period, provided that there is cyclical selection (Fig. 2*b*). This has a simple explanation. Suppose that a population is monomorphic and located at a distance $x$ from the midpoint of the selection cycle. Then, its geometric mean fitness is calculated to be

$$\bar{W}_g = \left( \prod_{t=1}^{L} \exp\left[ -s\left( x - A\sin\frac{2\pi t}{L} \right)^2 \right] \right)^{1/L} = \exp\left[ -\frac{s}{2}(A^2 + 2x^2) \right], \quad (5)$$

which is independent of the period $L$. (For a resting optimum, one has to set $A = 0$ in the final expression.) Assuming that $x = 0$, we obtain from Eqn 5 the values $\bar{W}_g = 0{\cdot}855$, $0{\cdot}535$ and $0{\cdot}082$ if $A = 0{\cdot}25$, $0{\cdot}5$ and 1, respectively. The numerically obtained values for the periods $L = 4, \ldots, 200$ are all between $0{\cdot}840$ and $0{\cdot}844$ if $A = 0{\cdot}25$, between $0{\cdot}526$ and $0{\cdot}529$ if $A = 0{\cdot}5$, and between $0{\cdot}081$ and $0{\cdot}082$ if $A = 1$. This good correspondence is not really surprising because, as our data suggest, most populations become monomorphic under periodic selection and, if they do not, then little variance is maintained on average. Also, the average mean genotypic value is always very close to the midpoint of the range of possible values (data not shown). The variation in geometric mean fitness among the genetic parameter sets pertaining to an ecological parameter set is tiny and not reported.

These results clearly do not support the proposition that periodic selection *per se* induces more genetic variation than constant stabilizing selection. However, as shown by the results of Kirzhner *et al.* (1996, 1998) and by the large standard deviations observed in the absence of mutation in the present study (Table 2), it can maintain substantial genetic variance for particular parameter combinations; its amount depends strongly on the underlying genetic system.

### (iii) *Role of mutation*

The introduction of mutation leads to a radically different conclusion. For a resting optimum ($L = 1$) and for short environmental periods ($L = 4$ or 8), mutation changes little. Of course, a high mutation rate leads to a somewhat elevated variance. For medium or long periods, even a low mutation rate leads to a substantial increase in genetic variance. The magnitude of this increase is strongly dependent on the amplitude of the fluctuations. For a small amplitude ($A = 0{\cdot}25$), the (relative) genetic variance increases with increasing period $L$, whereas, for a large amplitude ($A = 1$), there is marked peak in the genetic variance at intermediate periods ($L = 24$). If $A = 0{\cdot}5$, there is a strong increase in genetic variance if $8 \leqslant L \leqslant 52$; for longer periods the variance declines slightly (Fig. 2*a*). However, a glance at Table 2 reveals that, for every amplitude, the ratio of the variance with mutation to the variance without mutation is increasing on the whole range of periods. Only for $A = 1$ might a plateau be reached at periods of $L \geqslant 100$.

Interestingly, the magnitude of the mutation rate, unless very large, has only relatively weak quantitative effects, in the expected direction, of course. Fig. 3 displays the relative genetic variance as a function of $L$ for a wide range of mutation rates. For long periods, even the very small mutation rate of $u = 5 \times 10^{-7}$ leads to a strong increase in variance. As Figs. 2*b* and 3*b* show, for medium or long periods, the geometric average of mean fitness increases substantially with $L$ in the presence of mutation. The reason is that, with mutation, the population distribution can respond to the selective pressure induced by the moving optimum and follow, but lagging behind, the optimum (cf. Bürger & Lynch, 1995; Kondrashov & Yampolsky, 1996*a*; Bürger, 1999). For short periods, the direction of selection changes too rapidly for the population distribution to follow the optimum.

Among genetic parameter sets pertaining to a given ecological parameter set, there can be large variation in the (relative) genetic variance maintained. For the parameter sets displayed in Fig. 2, standard deviations

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of the relative genetic variance range from $\sim 10\%$ of the mean to 2·3 times the mean (Table 2). The highest values occur for a resting optimum and for low periods in combination with no or little mutation. Roughly, the standard deviation is decreasing as a function of $L$ and of $u$, but only weakly dependent on $A$. These results show that, for long periods and a positive mutation rate, the asymptotic dynamics is primarily driven by the selection cycle, with little variation between the genetic parameter sets. However, in the absence of mutation or for low mutation rates and short periods, the asymptotic properties of the evolving population, particularly the genetic variance maintained, depend strongly on the genetic details. The standard errors of the data displayed in Figs. 2 and 3 are $< 4\%$ of the mean in all cases and can be calculated from Table 2 by multiplication by $100/\sqrt{4000} \approx 1{\cdot}6$.

With mutation, the proportion of slow runs varies greatly. There is a tendency for this proportion to increase with lower mutation rates. For instance, for $u = 5 \times 10^{-6}$, nearly 9% of the runs are slow if $L \geqslant 100$, whereas, for $u = 5 \times 10^{-4}$, no slow runs are observed for large or small periods. However, for $u = 5 \times 10^{-5}$ and $u = 5 \times 10^{-4}$, the proportion of slow runs is maximized at intermediate periods, reaching nearly 5%, in the first case at $L = 52$, in the second at $L = 24$. Several of these slow runs showed complex limiting behaviour but, apparently, the variance (actually, this fluctuates much less than the gene frequencies, which might fluctuate wildly) does not deviate excessively from the average variance observed for such an ecological parameter set. For parameter combinations with a larger proportion of slow runs ($> 2\%$), the relative variance of the slow runs does not differ significantly from the total relative variance.

### (iv) *Strength of stabilizing selection and linkage*

For a trait determined by four loci and for the intermediate amplitude $A = 0{\cdot}5$, we now briefly investigate the role of the strength of stabilizing selection and of linkage, using the mutation rates $u = 0$ and $u = 5 \times 10^{-5}$. First, let us consider weak stabilizing selection ($s = 1$, so the fitness of the extreme genotypes is 0·78 if the optimum is at its midpoint (0·5)) and random recombination. For a resting optimum and in the absence of mutation, this yields nearly the same genetic variance as with strong stabilizing selection (Fig. 4). For quadratic selection, a similar observation was made by Bürger & Gimelfarb (1999). For increasing periods and without mutation, the (relative) genetic variance decreases, but much more slowly than under strong selection. Mutation ($u = 5 \times 10^{-5}$) increases the variance; not by very much for short and intermediate periods ($L \leqslant 52$), but by about a factor of 3·6 for $L = 100$ and 10·5 for $L = 200$. Still, these factors are much lower than in the case $s = 5$ (Table 2). Interestingly, in the presence of mutation and for the periods $L = 24$, 52 and 100, the relative variance $\bar{V}_r$ maintained under weak stabilizing selection is lower than under strong selection.

The role of linkage was investigated for strong selection ($s = 5$) and by setting the recombination rates between adjacent loci to 0·005 (no interference). Thus, in a genetic parameter set, only the allelic effects are randomly chosen. Fig. 4 shows that, in the absence of mutation, the variance is slightly elevated relative to the random recombination case. The reason might be that, with tightly linked loci, there is a tendency to maintain a higher proportion of loci polymorphic (this is known to happen in two-locus models of stabilizing selection; cf. Bürger & Gimelfarb, 1999). With mutation, the variance is substantially increased for periods $L \geqslant 24$, but there is a marked peak near $L = 52$, and increasing the period leads to a strong decline in genetic variance.

In the absence of mutation and for randomly drawn recombination rates, the average amount of linkage disequilibrium must be extremely low because the proportion of polymorphisms with two or more loci is very low (Table 1). Although not investigated in detail here, linkage disequilibrium is likely to be negative but low in the presence of mutation because of the relatively high average recombination rate (cf. Bürger, 1999).

The phenomenon that an evolving population with a high level of recombination might have a much higher genetic variance than an analogous population with little or no recombination was observed previously for traits determined by many mutable loci, both for a directionally moving optimum and for a periodic optimum (Kondrashov & Yampolsky, 1996*a*; Bürger, 1999; Bürger, 2000, Chap. VII). The likely reason is that, for such a moving optimum, adaptation (following the optimum) is essential. Low recombination reduces this ability because favourable mutations have a high probability of occurring in bad genomes, from which they can be effectively freed only by high recombination.

The qualitative behaviour of the geometric mean fitness is similar to that for strong stabilizing selection. In contrast to the case of random recombination, however, with tight linkage, $\bar{W}_g$ increases slightly for long periods in the absence of mutation.

### (v) *Number of loci*

Our results show that the asymptotic properties of a population subject to cyclical selection are strongly dependent on the number of loci that affect the trait. For a trait determined by two loci, the (relative) genetic variance maintained shows a qualitatively

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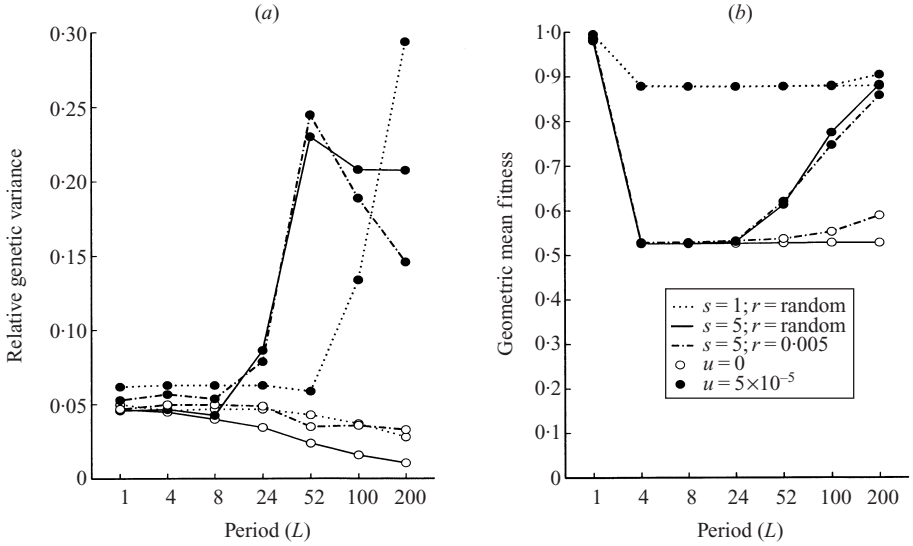


Fig. 4. The relative genetic variance (*a*) and the geometric mean fitness (*b*) under strong stabilizing selection ($s = 5$) and high (random) recombination are compared with the same quantities under weak stabilizing selection ($s = 1$) and random recombination, and under strong stabilizing selection and low recombination ($r = 0{\cdot}005$). The amplitude $A = 0{\cdot}5$, there are two mutation rates ($u = 0$ and $u = 5 \times 10^{-5}$) and no stochasticity in the optimum ($d = 0$).

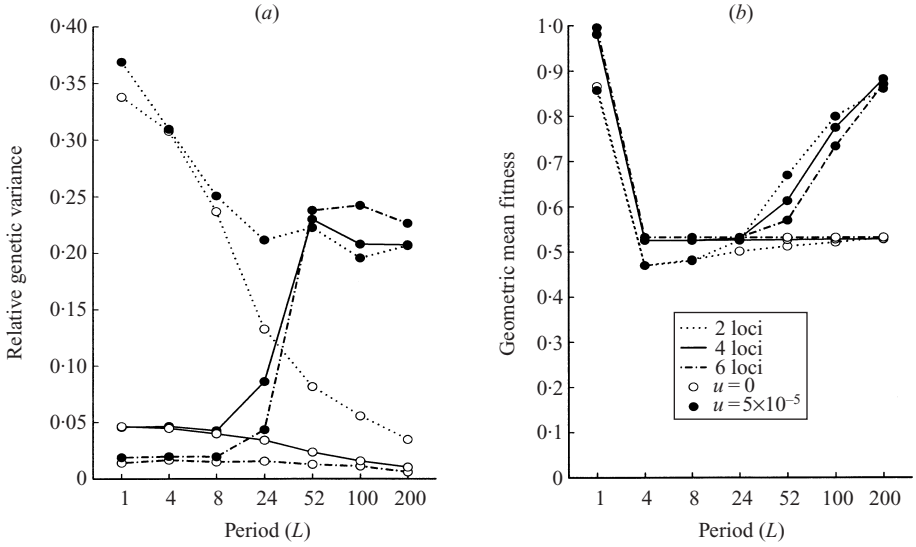


Fig. 5. (*a*) The relative genetic variance $\bar{V}_r$ as a function of the period $L$ for $n = 2$, 4 and 6 loci, without and with mutation ($u = 5 \times 10^{-5}$). (*b*) The corresponding geometric mean fitness $\bar{W}_g$. The strength of stabilizing selection is $s = 5$ in all cases and the position of the optimum varies purely periodically ($d = 0$).

different dependence on the parameters from a trait determined by four or six loci. The main results are displayed in Fig. 5. For all these parameter sets, the strength of stabilizing selection is $s = 5$, the amplitude is $A = 0{\cdot}5$ and recombination rates are random.

Most notably, for a resting optimum or for short periods, a much higher (relative) genetic variance is maintained in the two-locus model than with four or six loci. For a resting optimum, this phenomenon has already been reported and discussed in a detailed study of quadratic stabilizing selection (Bürger & Gimelfarb, 1999). In the two-locus model, the (relative) variance decreases rapidly with increasing period of the selection cycle, both with and without mutation. With mutation, however, the variance nearly levels out at large periods. In the absence of mutation, the variance in four- and six-locus models also decreases with increasing period, but much more slowly. Actually, the more loci that are contributing to the trait, the slower is the decay of genetic variance with increasing period: with six loci, about half as much variance is maintained at $L = 200$ as at $L = 1$; with four loci, this proportion is less than 0·25, and with two loci it is 0·10.

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By contrast, in the presence of mutation ($u = 5 \times 10^{-5}$) the highest increase in (relative) genetic variance at long periods occurs with six loci: for $L =$ 52, 100 and 200, the ratios of the relative genetic variance with mutation to that without mutation are about 18, 23 and 34, respectively; for four loci, the values are about 10, 13 and 20, respectively (Table 2); for two loci, they are 3, 3·5 and $\sim 6$. Interestingly, at long periods, the relative genetic variance maintained ranks according to the number of loci. However, even if the mutation rates in the two- and four-locus cases are increased such that the total (gametic) mutation rate affecting the trait is the same as with six loci, in no cases is the relative variance for two or four loci significantly higher than for six loci; the three values are closer together for every $L \geqslant 52$, the maximum difference being $< 10\%$ (results not shown).

For a trait determined by six loci, the standard deviation of the relative genetic variance among genetic parameter sets pertaining to a given ecological parameter set is very similar to that in the corresponding four-locus systems (Table 2). In the absence of mutation, it is $\sim 2{\cdot}5$ times the mean if $L =$ 1, 4 or 8, and decreases to $\sim 1{\cdot}7$ times the mean if $L = 200$. With mutation, the standard deviation decreases from $\sim 1{\cdot}7$ times the mean if $L = 1$ or 4 to $< 20\%$ of the mean if $L \geqslant 52$. Standard errors of $\bar{V}_r$ are $< 4\%$ of the mean for all data points displayed in Fig. 5. (Because the six-locus runs were extremely time consuming (more than a year of computer time on a 350 MHz Pentium III), the number of genetic parameter sets generated was adjusted to between 1000 and 4000, depending on the standard deviation of the variance.)

With six loci, and in the absence of mutation, slow convergence occurred in up to 4·6% of genetic parameter sets. Nevertheless, inclusion or exclusion of these runs led to nearly identical results. With mutation, the proportion of slow runs was $< 2{\cdot}5\%$ for $L \geqslant 100$, otherwise it was $< 0{\cdot}6\%$. Without mutation, the proportion of genetic parameter sets yielding asymptotic fixation of all loci was, as with four loci, close to 60%, except for $L = 200$, when it was 74%. The proportion of runs yielding polymorphisms involving two loci was below 1% in all cases, and polymorphisms involving three or more loci were never observed.

It has already been noted that the geometric average of mean fitness is remarkably constant as a function of $L$ provided that there is no mutation. With six loci, this constancy is even more pronounced (Fig. 5*b*). Indeed, $\bar{W}_g = 0{\cdot}533$ for all periods $L \geqslant 4$. If $x = 0$ then Eqn 5 yields the value 0·535. Again, the behaviour of the two-locus system is slightly aberrant. For reasons already discussed, in the presence of mutation, the geometric mean fitness increases with $L$ for any number of loci.

## 5. Randomly perturbed periodic environments

Random perturbations of a periodic optimum lead to some further interesting effects; in particular, mutation becomes even more decisive. The results in this section are based on a four-locus system with random recombination, an amplitude of $A = 0{\cdot}5$ and strong stabilizing selection ($s = 5$). Two levels of random perturbations were chosen: $d = 0{\cdot}5$ and $d = 1$. Hence, the standard deviations of the random perturbations are $0{\cdot}5A$ and $A$ (Eqn 3). Every ecological parameter set was combined with four different mutation rates ($u = 0$, $5 \times 10^{-6}$, $5 \times 10^{-5}$ and $5 \times 10^{-4}$). For each of these parameter combinations, 2000 genetic parameter sets were generated and the corresponding systems iterated for 50000 generations as described in the section on the statistical approach. Fig. 6 displays the main results and compares them with a deterministically moving periodic optimum ($d = 0$).

In the absence of mutation, the (relative) genetic variance maintained decays with the period $L$ and, for any given $L$, it decays with increasing stochasticity $d$. If $d = 1$, almost no genetic variance is maintained for any period. For a larger amplitude, adding stochasticity leads to an even higher loss of genetic variance (results not shown). Therefore, in the present model, there is always less variation maintained with a stochastically perturbed optimum than with a deterministic optimum (resting or cycling).

A completely different picture emerges with mutation. For the high-mutation-rate scenario ($u = 5 \times 10^{-4}$), the relative variance increases with $L$ if $1 \leqslant L \leqslant 8$, whereas, for the lower mutation rates, it is approximately constant within this range. Between $L = 8$ and $L = 52$, there is a marked increase in variance in all cases, and a maximum is reached at $L = 52$. For longer periods, the variance decreases slightly. Most interestingly, for short periods, a high degree of stochasticity ($d = 1$) induces substantial genetic variance in the presence of mutation, particularly for the two largest mutation rates. For long periods ($L \geqslant 24$), there is also a general tendency for more stochasticity to lead to slightly elevated levels of genetic variation.

Thus, with a periodic optimum, additional stochasticity depletes genetic variation in the absence of mutation. However, in the presence of mutation, even if of very low rate, it typically increases genetic variance. Therefore, mutation might be an important agent in promoting the maintenance of genetic variation in environments that fluctuate periodically with a random component. For mutable loci, it is also notable that the geometric mean fitness increases slower with $L$ in the presence of stochasticity than without stochasticity (Fig. 6*b*). The probable reason is that, with much stochasticity, a population is often displaced from the optimum, even if it could otherwise track a deterministically cycling optimum.

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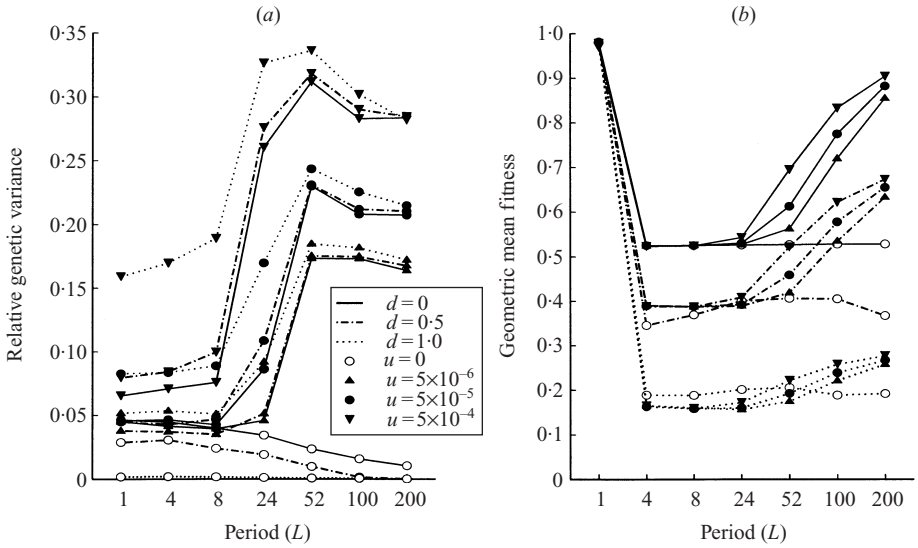


Fig. 6. The effects of random distortions of the position of the optimum on the relative genetic variance $\bar{V}_r$ (*a*) and on the geometric mean fitness $\bar{W}_g$ (*b*). The three indicated values of $d$ are combined with all four indicated values of the per-locus mutation rate $u$.

To find out if our populations have reached approximate stationarity after 50000 generations, iterations were performed for a subset of the parameters over 300000 and 500000 generations. In the presence of mutation, this yielded results that did not differ statistically significantly from the shorter runs. In the absence of mutation, however, the (relative) genetic variance was reduced, and substantially so (to 1/3) for large fluctuations ($d = 1$). The reason is that absorption of alleles might be a slow process with rare large random excursions of the optimum. Additionally, in the long runs and with $d = 1$, the geometric mean fitness was higher by up to 5% than in the short ones. Thus, in the absence of mutation, the variance maintained is lower than the data points in Fig. 6*a* indicate. Clearly, this strengthens our conclusions about the importance of mutation in stochastically fluctuating environments.

## 6. Discussion

Genetic models of temporally fluctuating selection have been investigated for a variety of reasons. First, to explore the potential of variable selection in maintaining genetic variation and polymorphism. Second, to examine the hypothesis that the evolution of recombination is favoured in changing environments. Third, to estimate the extinction risk of small populations through environmental change. In this article, we are only interested in the first of these topics and refer to Maynard Smith (1988), Charlesworth (1993), Kondrashov & Yampolsky (1996*b*), Korol *et al.* (1998), Bürger (1999) for the second, and to Bürger & Lynch (1995), Lande & Shannon (1996), Bürger (1999), and Bürger & Krall (2002) for the third.

Previous analyses of single-locus models in diploid, randomly mating, infinitely large populations have shown that, with fluctuating selection, the conditions for maintaining a protected polymorphism are relaxed compared with time-invariant selection because, roughly, overdominance of certain geometric averages of genotypic fitnesses is sufficient rather than overdominance of arithmetic averages (see Introduction). In general, even under deterministic cyclical selection, the asymptotic behaviour of gene frequencies is difficult to determine because several stable (periodic) equilibria, monomorphic and polymorphic can coexist. Because the conditions necessary for maintaining polymorphism are restrictive, fluctuating selection is unlikely to be a general cause for genetic variability. In finite populations, the situation is still more complex (Karlin & Levikson, 1974), and one of the topics that has received some attention is the comparison of models of temporally varying selection that is nearly neutral with models of neutral evolution (e.g. Takahata, 1981; Gillespie, 1991).

Recently, Kirzhner *et al.* (1996, 1998) have revived the hypothesis that temporally varying selection might be an important mechanism in maintaining genetic variation. They constructed several beautiful examples of multilocus systems in which stabilizing selection on a quantitative trait with a periodically changing optimum leads to various types of complex (sometimes chaotic) limiting behaviour of the gene and gamete frequencies. They conjectured that this might constitute a novel evolutionary mechanism increasing genetic diversity over long time periods.

We pursued a statistical approach to shed more light on cyclical selection as a possible source of genetic variation in quantitative traits. Our aim was to go beyond special results by investigating a fairly large

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region of ecological parameters and, for each set of such parameters, to obtain numerical results of many genetic systems. Our results show that, in the absence of mutation and on average, stabilizing selection with a periodic optimum never increases and, indeed, almost always decreases the genetic variance of a quantitative trait relative to that maintained under a resting optimum. Here, 'on average' means the average over genetic systems (typically, 2000 or 4000) in which the effects of the loci and the recombination rates between adjacent loci are drawn randomly, but the ecological parameters (strength of stabilizing selection, amplitude and period of the selection cycle, amount of stochasticity), the number of loci and the mutation rate are fixed.

Among the genetic systems pertaining to such a parameter combination, there might be large variation in the genetic variance maintained, and complex limiting behaviour was observed in some cases. Although we did cover a wide range of ecological parameters (weak and strong stabilizing selection, small to moderately large amplitudes, periods up to 200) and genetic systems with two, four and six additive loci, only a few of the examples provided by Korol *et al*. (1996) and Kirzhner *et al*. (1996, 1998) fall into this range. For additive loci, these authors reported complex limiting behaviour for very short selection cycles, typically of period two, for much stronger stabilizing selection than we investigated and for much larger amplitudes of the optimum. Thus, in their examples, many genotypes regularly have extremely low fitness, and the mean fitness of their populations is generally very low, typically $< 10\,\%$ of the maximum possible and often much less. For nonadditive loci, however, they observed complex limiting behaviour under much weaker selection. Interestingly, in our investigation, complex limiting behaviour was mainly observed for periods longer than 24. However, the proportion of parameter sets showing such behaviour was very small and the genetic variance maintained in such runs did not differ substantially from the average over all genetic parameter sets pertaining to the same combination of (ecological) parameters. Therefore, complex limiting behaviour, although it is an interesting phenomenon by itself, does not appear to be an important mechanism in maintaining quantitative genetic variation. It occurs for a relatively wide range of ecological parameters but requires special genetic constitution.

If, in addition to the cyclical variation, the optimum is stochastically perturbed then even more genetic variation is lost than without stochasticity, and, with large stochastic perturbations, almost none is left. We therefore conclude that, unless the genetic system has a particular structure, periodic and randomly perturbed periodic stabilizing selection on a quantitative trait is a powerful agent in depleting genetic variation.

If, however, the loci are subject to recurrent mutation, an almost opposite conclusion can be drawn because of the following findings.

1. Most notably, mutation, even if of very low rate, increases the genetic variance of a trait substantially, often by an order of magnitude or more, provided that the period of the selection cycle is moderate or long (typically $L \geqslant 24$). For shorter periods and in the absence of stochasticity, only high per-locus mutation rates ($u > 10^{-4}$) have a noticeable effect.
2. Whereas, in the absence of mutation, the genetic variance maintained decreases with increasing length of the selection cycle, the opposite is true in the presence of mutation provided that the amplitude is not too large and the loci are not tightly linked. In the latter two cases, the variance is maximized at intermediate periods.
3. The more loci are contributing to the trait, the more important becomes the effect of mutation. Without mutation, a general feature, valid for all considered parameter sets, is that the relative genetic variance (the average of $V/V_{\max}$) decreases with increasing number of loci. With mutation, this is not the case. In fact, for long periods ($L \geqslant 52$), the amount of relative genetic variance maintained is nearly independent of the number of loci, at least if between two and six loci contribute to the trait.
4. Stochastic perturbations of a periodic optimum reduce genetic variation in the absence of mutation but increase it otherwise. For short periods and high mutation rates, this increase can be substantial.

Therefore, as argued previously for populations of finite size and traits determined by many loci (Kondrashov & Yampolsky, 1996*a*, *b*; Bürger, 1999), long-term fluctuations of the environment of this or similar kind might indeed lead to substantially elevated levels of quantitative-genetic variation. The essential ingredients are a minimum amount of recurrent mutation, some recombination and periods of selection in one direction in excess of $\sim 10$ generations. Short-term or purely random fluctuations do not have this effect. The role of epistasis has not yet been explored in this context but, for pure stabilizing selection, some forms of epistasis can maintain much heritable variation (e.g. Gimelfarb, 1989).

There is a relatively simple qualitative explanation for the fact that substantial genetic variation is maintained in the presence of recurrent mutation and with moderate or long periods of the selection cycle. This can be understood from the following reasoning for a single diallelic locus under periodic selection. In the absence of mutation, a sufficient condition for the maintenance of a protected polymorphism is that the geometric mean fitness of both homozygotes (averaged

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over a full selection cycle) be lower than the corresponding value of the heterozygote (Haldane & Jayakar, 1963; Hoekstra, 1975). If the fitness function is as in Eqns 1 and 2, this condition is, in fact, necessary and sufficient (Appendix A2) and can be formulated as follows. Let the genotypic values at the locus under consideration be $0{\cdot}5+h-a$, $0{\cdot}5+h$ and $0{\cdot}5+h+a$ ($a>0$). Then, a protected polymorphism exists if and only if $a>2|h|$; that is, the heterozygote must have its genotypic value closer to the midpoint 0·5 of the selection cycle than any of the two homozygotes. Otherwise, the allele whose homozygous genotype is closer to 0·5 goes to fixation.

If periodic selection alone maintains a polymorphism or if one homozygous genotype is always inferior then, as for constant selection, low or moderate mutation rates increase the genetic variance only slightly. If, however, in the absence of mutation, no polymorphism is maintained in a one-locus system but each of the homozygotes has the highest fitness during part of the selection cycle, so that this locus is not exclusively under directional selection, then substantial genetic variance can be maintained with mutation and sufficiently long periods of the selection cycle, because recurrent mutation prevents allele frequencies of either type from becoming extremely low during periods in which the other allele is selectively favoured. Therefore, when the direction of selection changes, this allele can quickly rise in frequency, thus inducing much genetic variance. In such systems, allele frequencies typically vary substantially during the selection cycle, whereas in equivalent systems without mutation one of the alleles is lost. This is supported by numerical iterations of the recursion relations (results not shown). Because, with multiple loci, the fitness optimum experienced by a single locus depends on the genetic constitution of the other loci, single-locus heterozygotes are typically displaced from the midpoint 0·5, hence $|h|>0$ in the above model. Therefore, there is indeed the possibility for mutation to induce substantial variation. Presumably, this single-locus explanation extends to our multilocus systems as well, because the numerical results show that, in the absence of mutation, fewer than two loci are kept polymorphic in the vast majority of genetic systems.

The above considerations are also helpful for a qualitative understanding of some of the more detailed findings. For instance, the observation that, for long periods, mutation has the largest effect for traits determined by six loci has the following simple explanation. With an increasing number of loci, selection on each locus becomes weaker because the ratio of the average effect among polymorphic loci to the average effect among all loci decreases with increasing number of loci (Bürger & Gimelfarb, 1999). Therefore, with only few loci, long periods of directional selection drive the inferior alleles to lower frequency than with several loci, because the frequency at mutation–selection balance is inversely proportional to the selection intensity. However, under reversed selection pressure, recovering from extremely low frequency is a very slow process and the direction of selection might already have changed before the allele has made it to appreciable frequency. With many loci, gene frequencies apparently always remain in a range in which response to selection in any direction is quick.

## Appendix

For a trait determined by a single additive locus that is subject to periodic stabilizing selection according to Eqns 1 and 2, we derive a simple, necessary and sufficient condition for the maintenance of a protected polymorphism in the absence of mutation. We also give an example that, under general cyclical selection of period 2, three locally stable states can coexist: absorption of either of the two alleles and an interior limit cycle.

### (i) *One locus model*

We begin by recapitulating the model and main results of Hoekstra (1975), from which our results follow straightforwardly. As in the text, the population is infinitely large, mates at random and has discrete nonoverlapping generations. The relative fitnesses of the three genotypes $A_1A_1$, $A_1A_2$ and $A_2A_2$ in generations $t+kL$ ($t=1, 2, \ldots, L$, $k=1, 2, \ldots$) are denoted by $w_t$, 1 and $v_t$, respectively, and the relative frequency of allele $A_1$ is denoted by $p$. Then, $p=1$ (fixation of $A_1$) is a *linearly* stable equilibrium if and only if

$$P_w=\prod_{t=1}^{L} w_t>1, \tag{A1}$$

and $p=0$ is linearly stable if and only if

$$P_v=\prod_{t=1}^{L} w_t>1. \tag{A2}$$

Therefore, a sufficient condition for a protected polymorphism is that both

$$\prod_{t=1}^{L} v_t<1, \tag{A3a}$$

and

$$\prod_{t=1}^{L} w_t<1, \tag{A3b}$$

are satisfied.

Let $f_L(p)$ denote the function that assigns to $p$ the frequency of $A_1$ after $L$ generations if, without loss of generality, the fitnesses in the initial generation are $w_1$,

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1 and $v_1$. (Notice that $f_L(p) = g_L(g_{L-1}(\ldots g_1(p)))$, where $g_i(p) = p'$ if the fitnesses are $w_i$, 1, $v_i$.) If $P_w = 1$ (i.e. $A_1$ is completely dominant) then the second derivative of $f_L(p)$ determines the local stability of $p = 1$. Applying the chain rule and using $g_i(1) = 1$ for all $i$, one obtains, after some rearrangement (Hoekstra, 1975)

$$\left.\frac{d^2 f_L}{dp^2}\right|_{p=1} = 2P_w^{-2}\left[2(1-P_w)+\sum_{j=1}^{L}(1-v_j)\prod_{t=j}^{L} w_t\right]. \quad \text{(A4)}$$

Thus, if $P_w = 1$ then $p = 1$ is locally stable if and only if this derivative is positive, which is the case if and only if

$$\sum_{j=1}^{L}(1-v_j)\prod_{t=j}^{L} w_t > 0. \quad \text{(A5)}$$

An analogous condition, with $v$ and $w$ exchanged, holds at $p = 0$.

(ii) *Application to our model*

We now apply this theory to a generalized one-locus version of our model in which it is not assumed that the heterozygote coincides with the midpoint 0·5 of the selection cycle. Let the effects of the genotypic values of $A_1A_1$, $A_1A_2$ and $A_2A_2$ be $0{\cdot}5+h-a$, $0{\cdot}5+h$ and $0{\cdot}5+h+a$, respectively, where $a > 0$. The fitnesses of the three genotypes can then be computed from Eqns 1 and 2. After normalizing the fitnesses of the heterozygote to 1 in each generation, we obtain

$$w_t = \exp[-as(a-2h)]\exp\left[-2asA\sin\frac{2\pi t}{L}\right], \quad \text{(A6a)}$$

and

$$v_t = \exp[-as(a+2h)]\exp\left[2asA\sin\frac{2\pi t}{L}\right], \quad \text{(A6b)}$$

and a further simple calculation yields

$$P_w = \exp[-asL(a-2h)], \quad \text{(A7a)}$$

$$P_v = \exp[-asL(a+2h)]. \quad \text{(A7b)}$$

Using

$$v_t\prod_{t=j}^{L} w_t = e^{-2a^2 s}\prod_{t=j+1}^{L} w_t,$$

and observing

$$\sum_{j=1}^{L}\prod_{t=j+1}^{L} w_t = \sum_{j=1}^{L}\prod_{t=j}^{L} w_t + 1 - P_w,$$

we obtain

$$\sum_{j=1}^{L}(1-v_j)\prod_{t=j}^{L} w_t = \sum_{j=1}^{L}\prod_{t=j}^{L} w_t - e^{-2a^2 s}\sum_{j=1}^{L}\prod_{t=j+1}^{L} w_t$$

$$= (1-e^{-2a^2 s})\sum_{j=1}^{L}\prod_{t=j}^{L} w_t + e^{-2a^2 s}(P_w - 1).$$

From Eqn A4, we can now infer that

$$\left.\frac{d^2 f_L}{dp^2}\right|_{p=1} > 0 \text{ if } P_w = 1,$$

if $P_w = 1$. (In fact, the same conclusion can be shown to be valid whenever $P_w < 1+\epsilon$ for an appropriate $\epsilon > 0$). Hence, in this model, there are trajectories converging to the boundary $p = 1$ ($p = 0$) if and only if $P_w \geqslant 1$ ($P_v \geqslant 1$). Then, the boundaries are also asymptotically stable.

Therefore, we can conclude the following:

1. There is a protected polymorphism if and only $a > 2|h|$; that is, if and only if the value of the heterozygote is closer to 0·5 than any of the homozygous genotypic values. Numerical computations of $f_L(p)$, as well as iterations of the recursion relation, suggest that, in this case, all trajectories converge to a uniquely determined limit cycle of period $L$.
2. If $h > 0$ and $a \leqslant 2h$ then $p = 1$ is locally stable and $p = 0$ is unstable. Numerical computations of $f_L(p)$ suggest that, in this case, $p = 1$ is always globally stable; that is, allele $A_1$ always becomes fixed.
3. If $h < 0$ and $a \leqslant -2h$, then $p = 0$ is locally stable and $p = 1$ is unstable. Apparently, $p = 0$ is globally stable.

(iii) *An example of multiple stable equilibria*

Following a suggestion by J. Hofbauer, we show that, in the general one-locus model with cyclical selection and only two environments ($L = 2$), up to three stable (periodic) equilibria may coexist. The idea is to perturb fitnesses that satisfy $w_1 w_2 = 1$ and $\sum_{j=1}^{2}(1-v_j)\prod_{t=j}^{2} w_t < 0$ (thus, $p = 1$ is linearly neutral but quadratically unstable) such that both

$$w_1 w_2 = 1 \quad \text{(A8a)}$$

and

$$\sum_{j=1}^{2}(1-v_j)\prod_{t=j}^{2} w_t < 0 \quad \text{(A8b)}$$

hold. Then, $p = 1$ is stable and an unstable fixed point of $f_2$ should exist for $p < 1$ because $f_2$ is concave near $p = 1$. The same can be done with $v_1$ and $v_2$.

Indeed, choosing $w_1 = 0{\cdot}52$, $v_1 = 1{\cdot}0$, $w_2 = 1{\cdot}94$ and $v_2 = 1{\cdot}1$ yields the desired numerical example: local stability of the boundaries $p = 0$ and $p = 1$, and local stability of the periodic equilibrium $\hat{p}(1) = 0{\cdot}686$ and $\hat{p}(2) = 0{\cdot}777$. If the initial fitnesses are $w_1$ and $v_1$ then every trajectory starting in the interval $(0, 0{\cdot}308)$ converges to 0, every trajectory starting in $(0{\cdot}934, 1)$ converges to 1 and all others converge to the interior limit cycle. If the initial fitnesses are $w_2$ and $v_2$ then trajectories from $(0, 0{\cdot}275)$ converge to 0 and those from $(0{\cdot}886, 1)$ converge to 1. This can be proved

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straightforwardly by studying the numerator of $f_2(p)$ that is a polynomial of degree five. Because it has the two zeroes $p = 0$ and $p = 1$, the problem is reduced to analysing a polynomial of degree three.

For cyclical selection with period $L \geqslant 3$, examples with more attractors should be constructible. More complicated attractors than periodic orbits cannot occur with two alleles because the map $f_1(p)$ $(= p')$ is monotonic for any choice of fitness values. Therefore, all iterates, in particular $f_L(p)$, are monotonic (cf. Hofbauer & Sigmund, 1998, p. 241).

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