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IIASA Interim Report
August 2002

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Interim Report **IR-02-058**

Fluctuating Environments and the Role of Mutation in Maintaining Quantitative Genetic Variation

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August 2002

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Contents

Abstract

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 may 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 in maintaining quantitative-genetic variation. Whereas, in contrast to some recent claims, this potential seems to be rather limited in the absence of recurrent mutation, in combination with it fluctuating environments may frequently generate high levels of additive genetic variation. It is investigated how the genetic variation maintained depends on the ecological parameters and on the underlying genetics.

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Acknowledgements

R.B. thanks J. Hofbauer for pointing out how the example in Appendix A.3 can be constructed. Part of this work was performed while R.B. was visiting the Adaptive Dynamics Network of the International Institute of Applied Systems Analysis (IIASA) in Laxenburg, Austria. Its hospitality is gratefully acknowledged. This visit was funded by a grant from the Austrian Ministry of Science.

Fluctuating Environments and the Role of Mutation in Maintaining Quantitative Genetic Variation

Reinhard Bürger
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1 Introduction

Populations inhabit environments that are not uniform, but may be structured and variable in time or space. Most individuals within a local subpopulation will experience similar environmental conditions changing on time scales below one 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 may 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 fluctuating between generations. The causes of such fluctuations may be manifold, ranging from changes in the abiotic environment to variation in the density of other, ecologically relevant, species, but 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 and 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 to be unsettled 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) be lower than the corresponding value of the heterozygote. Also in the case of complete dominance such sufficient conditions have been found (Haldane and Jayakar 1963, Hoekstra 1975; see Appendix A.1 for a brief summary). A complete characterization of the limiting behavior has been obtained only for very simple models of cyclical selection (e.g., Karlin and Liberman 1974, Nagylaki 1975); in general diallelic one-locus systems under cyclical selection, multiple stable (periodic) equilibria may coexist (see Appendix A.3). Kirzhner et al. (1995) showed that in one-locus models with four alleles and cyclical selection of period two, so-called supercycles can exist. These are cycles with a period that may be much (hundreds of times) longer than that of the selection cycle. Hence,

even in one-locus systems, there is little hope for establishing 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, whereas otherwise fixation of one or the other allele may occur; but this can be a very slow process (cf., Hoekstra 1975).

In a series of papers, Kirzhner and colleagues investigated the possibility of maintaining genetic polymorphism in multilocus models under cyclical selection. In Kirzhner et al. (1996), general conditions are derived for the stability of polymorphisms in two-locus models of cyclical selection. 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 fitness than all other genotypes. Most interestingly, they found that rather simple periodic changes can lead to extremely complex dynamic behavior of the gamete frequencies, such as chaotic-like attractors or supercycles. Such complex limiting behavior 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) or up to six loci (Kirzhner et al. 1996, 1998) and is under stabilizing selection with a periodically moving optimum. These authors promoted the hypothesis that cyclic environmental change may be an important factor in maintaining genetic polymorphism (Korol et al. 1996, Kirzhner et al. 1998). They also showed that nonadditive gene interaction may relax the conditions for protected polymorphisms (Kirzhner et al. 1998). For brief summaries of empirical studies of cyclical and fluctuating selection we refer to Korol et al. (1996) and to Kondrashov and Yampolsky (1996a). In this empirical literature indications are found for an association between temporal environmental heterogeneity and the amount of genetic variation, but little conclusive evidence. One of the reasons for this lack of evidence may 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 and Yampolsky (1996a) and Bürger (1999) on a very similar model. The latter 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 or less generations neither Kondrashov and Yampolsky (1996) nor Bürger (1999) found a detectable increase in genetic variation. The work of these authors differs from that of Kirzhner and colleagues in as far as in their models 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. It has not been explored to what extent the high levels of genetic variation maintained in the models of Kondrashov and Yampolski, and Bürger depend on the presence of recurrent mutation.

Random temporal variation in fitness has also been studied. For a single diallelic locus, Karlin and 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., 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 fitness of the heterozygotes. However biologically, this condition is not sufficient to ensure a protected polymorphism because temporarily the allele can 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 analyzed by means of diffusion approximation may be found in Gillespie (1991). Although these models are designed to study molecular evolution, they share much in common with some standard quantitative-genetic models. In summary, with stochastically fluctuating fitnesses, genetic variation can be maintained in situations in which this were impossible for constant fitnesses that coincide with the respective expectations; in particular models much variation can be maintained.

For quantitative-genetic models in which in each generation the position of the optimum fluctuates randomly across generations without autocorrelation, for instance, such that in each generation the position of the optimum is drawn from a normal distribution, no or only 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 and Turelli 1989); see also Zonta and 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 may be increased by an increasing genetic variance, thus suggesting that this kind of temporal variation in fitness has the potential of increasing genetic variation provided the genetic system is flexible enough (Slatkin and Lande 1976, Charlesworth 1993, Lande and 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 may 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, thus implying a kind of soft selection.

In this article we explore the potential of fluctuating selection for maintaining genetic variation in quantitative traits in the absence and presence of recurrent mutation. The diploid population has discrete nonoverlapping generations, is infinitely large, and randomly mating. The trait is under stabilizing selection with an optimum

that changes periodically, with or without random distortions, and it 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), given number of loci and given mutation rate, the recursion relations are iterated for a large number of randomly chosen sets of genetic parameters (allelic effects and recombination rates) until stationarity is reached. Then the quantities of interest are measured. In this way, the average asymptotic geometric mean fitness, the average asymptotic genetic variance, etc., are obtained for each set of parameters. In the absence of mutation we find that almost any such kind of 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 a number of interesting phenomena.

2 The General Model

In an infinite, randomly mating diploid population, a quantitative character is considered that is controlled additively by n diallelic loci. The contribution of one allele at each locus ℓ is zero, and the contribution, β_ℓ, of the other allele is a random number between zero and one. It is assumed that the minimum and maximum genotypic values are always zero and one. Therefore, the actual contribution by the second allele at locus ℓ is scaled to be $\alpha_\ell = \frac{1}{2}\beta_\ell / \sum_{k=1}^{n} \beta_k$. This implies that the genotypic value of the total heterozygote is always $\frac{1}{2}$, and the average allelic effect among the n loci controlling the trait is $\overline{\alpha} = 1/(2n)$. 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 were a deflation of the selection intensity.

The trait is under Gaussian stabilizing selection, with the optimum genotype θ_t exhibiting temporal change, i.e., the viability of an individual with genotypic value G is assumed to be

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

where s measures the strength of stabilizing selection and is independent of the generation number t. Selection acts only through differential viabilities. The position of the optimum is assumed to fluctuate periodically about the midpoint ($\frac{1}{2}$) of the range of genotypic values; in addition, its position may be randomly perturbed. More precisely, we assume that θ_t is drawn from a normal distribution with mean

$$\theta_t = \tfrac{1}{2} + A\sin(2\pi t/L) , \tag{2}$$

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 for the magnitude of stochasticity. If $d = 0$, there is purely periodic selection; if in addition $A = 0$, then there is pure Gaussian stabilizing selection. The reason that the 'noise term' (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 such with large amplitudes. Figure 1 visualizes 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} (we omit 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, i.e., 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 of the distribution of gametes under viability selection followed by recombination and mutation is given by

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

where

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

denotes the frequency of gamete i after selection and recombination, and $\overline{W} = \sum_{j,k} W_{jk} p_j p_k$ is the mean fitness (see, e.g., Bürger 2000).

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

3 The Statistical Approach

Usually, parameters of genetic systems controlling quantitative traits are unknown or can be inferred only indirectly. Since, 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 used a different approach by evaluating the quantities of interest for randomly chosen parameter sets and initial conditions, and, consequently, obtaining statistical results.

We proceeded as follows. For a given set of *ecological* parameters (strength s of stabilizing selection, amplitude A and period L of the selection cycle, 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 to 4000, what we shall call, *genetic parameter sets* (allelic effects of loci and recombination rates between adjacent loci).

For each genetic parameter set, allelic effects were obtained by generating values β_ℓ ($\ell = 1, 2, \ldots, n$) as independent random variables, uniformly distributed between

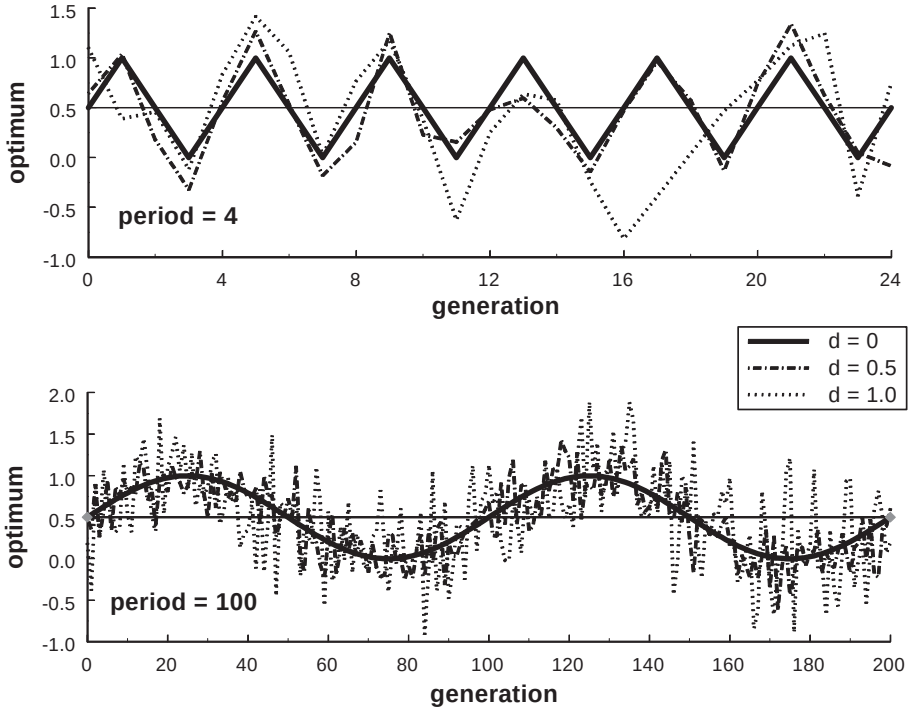

Figure 1: Displayed is the movement of a cyclically fluctuating optimum without and with random perturbations according to eqs. (2) and (3). The amplitude is $A = 0.5$ in both cases, the upper panel is for a period of $L = 4$, the lower for $L = 100$. The values of the parameter d, measuring the amount of stochasticity, are as used below; if $d = 0$, the optimum is purely periodic; if $d = 1$, there are substantial random perturbations of its deterministic position.

0 and 1, and transforming them into the actual allelic effects, $\alpha_\ell = \frac{1}{2}\beta_\ell / \sum_k \beta_k$. The additivity assumption yields the genotypic values, and from equations (1) – (3), the genotypic fitnesses W_{jk} are calculated in each generation. Recombination rates between adjacent loci, $r_{\ell,\ell+1}$ ($\ell = 1, \ldots, n-1$), were obtained as independent random variables, uniformly distributed between 0 and $\frac{1}{2}$. 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), thus only allelic effects were chosen randomly. In all cases did we assume no interference.

For each of such constructed genetic parameter sets, the recursion relations (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 cycles, $\left(\sum_i |p_i(t+L) - p_i(t)|^2\right)^{1/2}$ with t a multiple of L, is less than 10^{-12}), or t exceeded 300,000 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 oc-

cur within 300,000 generations: (i) slow convergence or (ii) no periodic solution is approached. Inspection of the output showed that in the majority of cases, slow convergence was the likely reason why an iteration exceeded 300,000 generations. But in a number of cases, trajectories indeed showed complex dynamic behavior, similar to what Kirzhner and colleagues observed (see the references in 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 $\overline{V}$ of the genetic variances, arithmetic average $\overline{V}_{\mathrm{r}}$ 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 $\overline{W}_{\mathrm{g}}$ of population mean fitness. Also the number of polymorphic loci was 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 $\overline{V}_{\mathrm{r}}$ 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 among loci, which decreases according to $1/(2n)$. For a given number of loci, the relative genetic variance $\overline{V}_{\mathrm{r}}$ and the real (average) genetic variance $\overline{V}$ behave very similar (results not shown). Because $V_{\max} = \frac{1}{2}\sum_i \alpha_\ell^2$, the expectation (and in principle the whole distribution) of $V_{\max}$ can be calculated for each n. For instance, if $n = 4$, we have $E[V_{\max}] = \frac{1}{4}(1 - 44\ln 2 + 27\ln 3) \approx 0.041$. For $n = 2$ and $n = 6$, the respective numerical values are 0.077 and 0.028. Multiplying $\overline{V}_{\mathrm{r}}$ by $E[V_{\max}]$ yields an estimate of $\overline{V}$ that typically is smaller, 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 300,000 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, the slow runs had to be 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 50,000 generations and averaged all quantities of interest over the final 10 selection cycles. Comparison with additional computations for some selected parameter sets over 300,000 or 500,000 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) The Basic Data Set

For this basic data set, we consider a trait determined by $n = 4$ 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 $\exp(-\frac{5}{4}) \approx 0.287$. For every combination of the parameters $L = 1$, 4, 8, 24, 52, 100, 200, $A = 0.25$, 0.5, 1, and $u = 0$, 5×10^{-6}, 5×10^{-5}, 5×10^{-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 $\frac{1}{2}$. 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 $A = 0.5$ means that the optimum cycles between the most extreme genotypes; thus there always exists a genotype that is close to the optimum. It is only for $A = 1$ that there are periods of directional selection, namely when the optimum is outside the range of possible genotypic values. The main results are summarized in Tables 1 and 2, and in Figures 2 and 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 about 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 is 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 less than 2%, the frequency of parameter sets maintaining three loci polymorphic is less than 0.3%, and in no instance was a four-locus polymorphism observed. Thus the most likely event is that all loci go to fixation; otherwise, in almost all cases a single locus remains polymorphic.

As Table 2 and Figure 2a show, in the absence of mutation the relative genetic variance decreases monotonically with increasing length of the period. For

Table 1: Equilibrium structure under periodic selection in the absence of mutations. Displayed is the percentage of (stable) equilibria with the given number of polymorphic loci in a four-locus system without mutation and 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 0.00 indicates that the corresponding frequency is less than 0.005, an entry – indicates that this outcome was never observed.

environment		polymorphic loci				slow
A	L	0	1	2	3	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

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 ($L = 4, 8$) 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, slow runs occurred in which the iterations did not equilibrate within 300,000 generations. In the absence of mutation, their fraction was about 1% (Table 1). In some of these slow runs, apparently complex limiting behavior 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 contradistinction to the conclusions of Kirzhner et al. (1996, 1998), our results suggest that complex limiting behavior occurs at nonnegligible frequency only in carefully selected regions of the parameter space, at least if loci are additive and selection is not extremely strong.

Table 2: Effect of mutation on the relative genetic variance $\overline{V}_r$. For four-locus systems, $s = 5$, and the indicated amplitudes and periods, column 3 displays the arithmetic average , $\overline{V}_r$ 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 deviation of $\overline{V}_r$ for the indicated mutation rates in multiples of $\overline{V}_r$.

environment		$\overline{V}_r\,(\mu=0)$	$\overline{V}_r(\mu)\,/\,\overline{V}_r(\mu=0)$			st. dev. of $\overline{V}_r(\mu)$			
A	L		5×10^{-6}	5×10^{-5}	5×10^{-4}	$\mu=0$	5×10^{-6}	5×10^{-5}	5×10^{-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

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

$$\overline{W}_{\rm g} = \left(\prod_{t=1}^{L} \exp\left[-s\Big(x - A\sin\frac{2\pi t}{L}\Big)^2\right]\right)^{1/L} = \exp\left[-\frac{s}{2}(A^2+2x^2)\right] \ , \qquad (5)$$

which is independent of the period L. (For a resting optimum one has to set $A = 0$ in the final expression.) Assuming $x = 0$, we obtain from (5) the values $\overline{W}_{\rm g} = 0.855$, 0.535, 0.082 if $A = 0.25$, 0.5, 1, respectively. The numerically obtained values for the periods $L = 4, \ldots, 200$ are all between 0.840 and 0.844 if $A = 0.25$, between 0.526 and 0.529 if $A = 0.5$, and between 0.081 and 0.082 if $A = 1$. This good correspondence is not really surprising because, as our data suggest, the majority

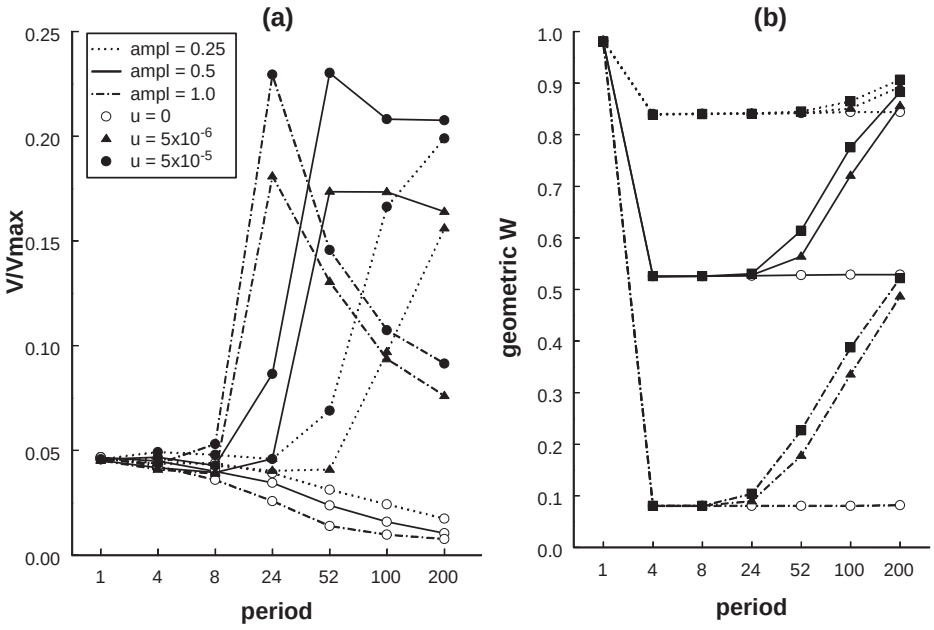

Figure 2: Figure 2a displays the relative genetic variance $\overline{V}_{\rm r}$, i.e., the arithmetic average of $V/V_{\rm max}$, for all combinations of the three indicated mutation rates and the three amplitudes as a function of the period of the selection cycle. Figure 2b contains the corresponding curves for the geometric average of mean fitness, $\overline{W}_{\rm g}$. The strength of stabilizing selection is $s = 5$ in all cases, and the position of the optimum is purely periodic ($d = 0$).

of populations becomes monomorphic under periodic selection, and if not, then on average only little variance is maintained. 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), for particular parameter combinations it can maintain substantial genetic variance; its amount depends strongly on the underlying genetic system.

(iii) The Role of Mutation

The introduction of mutation leads to a radically different conclusion. For a resting optimum ($L = 1$) and for short environmental periods ($L = 4, 8$), 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 ($A = 0.25$), the (relative) genetic variance increases with increasing period L, whereas for a large amplitude

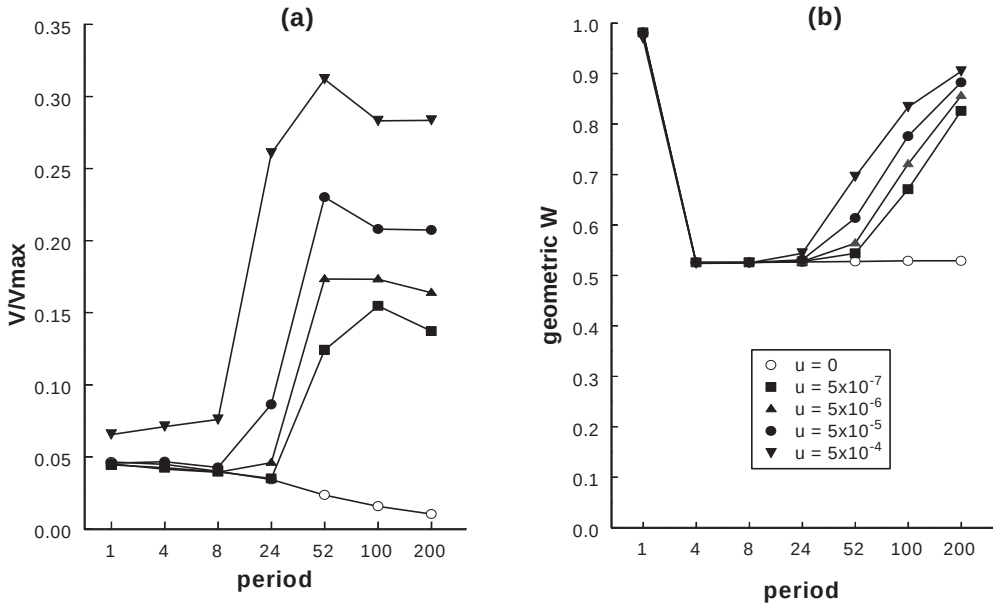

Figure 3: Similar to Figure 2, but the effect of mutation is shown for a much larger range of mutation rates. We have $A = 0.5$, $s = 5$, and $d = 0$.

($A = 1$), there is marked peak in the genetic variance at intermediate periods ($L = 24$). If $A = 0.5$, there is a strong increase in genetic variance if $8 \leq L \leq 52$, and for larger periods the variance declines slightly (Figure 2a). A glance at Table 2 reveals however 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 $A = 1$ may a plateau be reached at periods of $L \geq 100$.

Interestingly, the magnitude of the mutation rate, unless very large, has only relatively weak quantitative effects, in the expected direction, of course. Figure 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 Figures 2b and 3b 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 and Lynch 1995, Kondrashov and Yampolsky 1996a, 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 may be large variation in the (relative) genetic variance maintained. For the parameter sets displayed in Figure 2, standard deviations of the relative genetic variance range from about 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. But in the absence of mutation or for low mutation rates and short periods, the asymptotic properties of the evolving population, in particular, the genetic variance maintained, depend strongly on the genetic details. The standard errors of the data displayed in Figures 2 and 3 are less than 4% of the mean in all cases, and can be calculated from Table 2 by multiplication with $100/\sqrt{4000} \approx 1.6$.

With mutation, the proportion of slow runs varies greatly. There is a tendency that with lower mutation rates this proportion increases. For instance, for $u = 5 \times 10^{-6}$, nearly 9% of the runs are slow if $L \geq 100$, 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 behavior, but apparently the variance (actually, fluctuating much less than the gene frequencies, which may 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 (more than 2%), the relative variance of the slow runs does not differ significantly from the total relative variance.

(iv) The Strength of Stabilizing Selection and Linkage

For a trait determined by four loci and for the intermediate amplitude $A = 0.5$, we now briefly investigate the role of the strength of stabilizing selection and of linkage. We choose the mutation rates $u = 0$ and $u = 5 \times 10^{-5}$.

First, let us consider weak stabilizing selection ($s = 1$; then the fitness of the extreme genotypes is 0.78 if the optimum is at its midpoint $\frac{1}{2}$) 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; see Figure 4. For quadratic selection a similar observation was made by Bürger and 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 ($L \leq 52$), 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 $s = 5$ (cf. Table 2). Interestingly, in the presence of mutation and for the periods $L = 24, 52, 100$, the relative variance $\overline{V}_{\mathrm{r}}$ 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. Figure 4 shows that in the absence of mutation the variance is slightly elevated relative to the random recombination case. The reason may be that with tightly linked loci, there is a tendency of maintaining a higher proportion of loci polymorphic (this is known to happen in two-locus models of stabilizing selection; cf. Bürger and Gimelfarb 1999). With mutation, the variance is substantially increased for periods $L \geq 24$, but there is a marked peak near $L = 52$ and increasing the period leads to a strong decline of genetic variance.

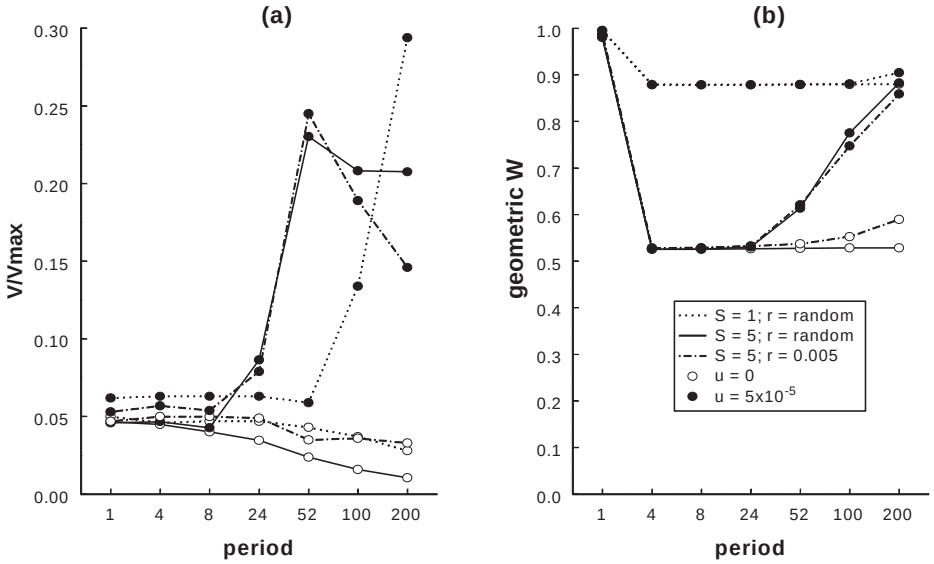

Figure 4: The relative genetic variance (a) and the geometric mean fitness (b) under strong stabilizing selection ($s = 5$) and high (random) recombination are compared with the respective quantities under weak stabilizing selection ($s = 1$) and random recombination, and under strong stabilizing selection and low recombination ($r = 0.005$). The amplitude is $A = 0.5$, there are two mutation rates ($u = 0, 5 \times 10^{-5}$), and no stochasticity in the optimum ($d = 0$).

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 may 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 and Yampolsky 1996a, Bürger 1999, Bürger 2000, Chap. VII). The likely reason is that for such a moving optimum, adaptation, i.e., following the optimum, is essential. Low recombination reduces this ability because favorable mutations have a high probability of occurring in bad genomes, from which they can be effectively freed only by high recombination.

The qualitative behavior 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 $\overline{W}_{\mathrm{g}}$ increases slightly for long periods in the absence of mutation.

(v) The 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 different dependence on the parameters from a trait determined by four or six loci. The main results are displayed in Figure 5. For all these parameter sets, the strength of stabilizing selection is $s = 5$, the amplitude is $A = 0.5$, and recombination rates are random.

Most notably, for a resting optimum or for short periods, in the two-locus model a much higher (relative) genetic variance is maintained than with four or six loci. For a resting optimum, this phenomenon was already reported and discussed in a detailed study of quadratic stabilizing selection (Bürger and 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 slower. Actually, the more loci 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 $L = 200$ than at $L = 1$; with four loci this fraction is less than $\frac{1}{4}$, and with two loci it is $\frac{1}{10}$.

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 $L = 52, 100, 200$, the ratios of the relative genetic variance with mutation to that without mutation are about 18, 23, 34, respectively; for four loci the respective values are about 10, 13, 20 (see Table 2), for two loci they are 3, 3.5, and 6. Interestingly, at long periods the relative genetic variance maintained ranks according to the number of loci. However, even if the mutation rate in the two- and four-locus case is increased such that the total (gametic) mutation rate affecting the trait is the same as with six loci, in none of these cases is the relative variance for two or four loci statistically significantly higher than for six loci. Then the three values are closer together for every $L \geq 52$, the maximum difference being less than 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 (cf. Table 2). In the absence of mutation, it is about 2.5 times the mean if $L = 1, 4, 8$, and decreases to about 1.7 times the mean if $L = 200$. With mutation, the standard deviation decreases from about 1.7 times the mean if $L = 1, 4$ to less than 20% of the mean if $L \geq 52$. Standard errors of $\overline{V}_\mathrm{r}$ are less than 4% of the mean for all data points displayed in Figure 5. (Because the six-locus runs were extremely time consuming, all together more than a year of running on a Pentium III with 350 MHZ, the number of generated genetic parameter sets was adjusted 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 less than 2.5% for $L \geq 100$, otherwise less than 0.6%.

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

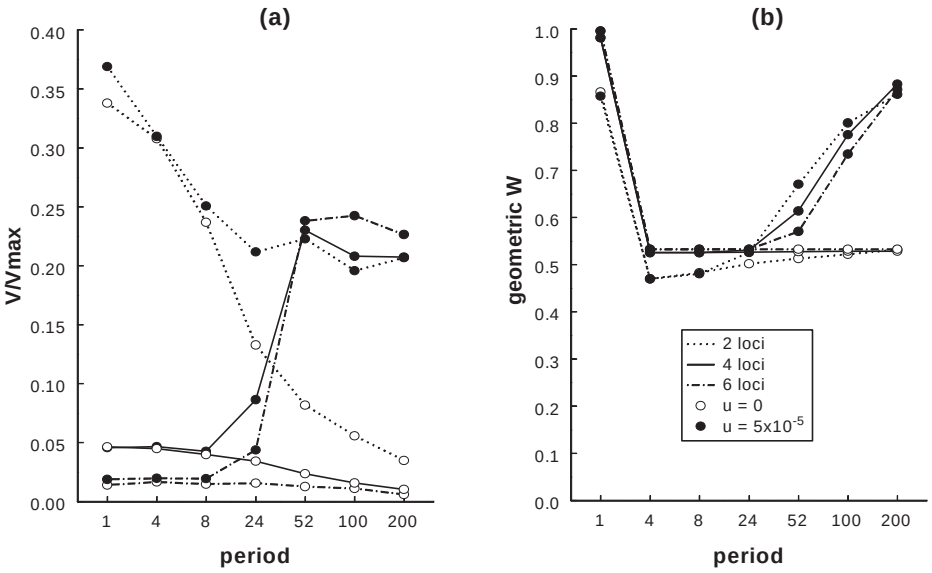

Figure 5: Figure 5a shows the relative genetic variance $\overline{V}_{\rm r}$ as a function of the period L for $n = 2, 4, 6$ loci, without and with mutation ($u = 5 \times 10^{-5}$). Figure 5b shows the corresponding geometric mean fitness $\overline{W}_{\rm g}$. The strength of stabilizing selection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

below 1% in all cases, and polymorphisms involving three or more loci were never observed.

It was already noted above that the geometric average of mean fitness is remarkably constant as a function of L, provided there is no mutation. With six loci, this constancy is even more pronounced (see Fig. 5b). Indeed, $\overline{W}_{\rm g} = 0.533$ for all periods $L \geq 4$. If $x = 0$, then eq. (5) yields the value 0.535. Again, the behavior 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 $A = 0.5$, and strong stabilizing selection ($s = 5$). Two levels of random perturbations were chosen: $d = 0.5$ and $d = 1$, hence the standard deviations of the random perturbations are $\frac{1}{2}A$ and A; cf. eq. (3). Every ecological parameter set was combined with four different mutation rates ($u = 0$, 5×10^{-6}, 5×10^{-5}, 5×10^{-4}). For each of these parameter combinations, 2000 genetic parameter sets were generated and the corresponding systems iterated for 50,000 generations as described in the section on the statistical approach. Figure 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

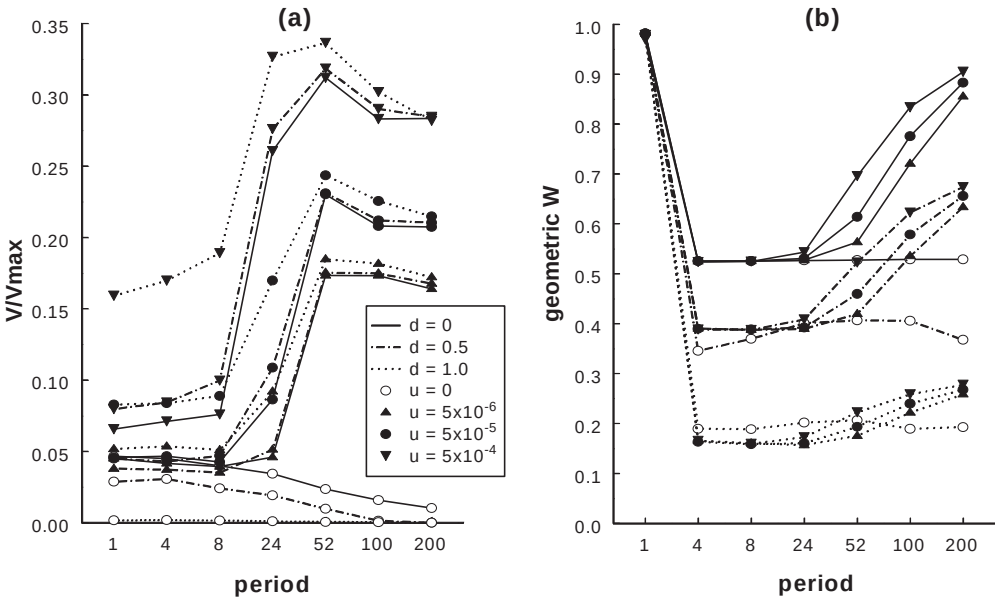

Figure 6: This figure demonstrates the effects of random distortions of the position of the optimum on the relative genetic variance $\overline{V}_{\rm r}$ (a) and on the geometric mean fitness $\overline{W}_{\rm g}$ (b). The three indicated values of d are combined with all four indicated values of the per-locus mutation rate u.

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 already if $1 \leq L \leq 8$, whereas for the smaller mutation rates it is approximately constant on this range. Between $L = 8$ and $L = 52$ a marked increase in variance occurs 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, in particular, for the two largest mutation rates. For long periods ($L \geq 24$), there is also a general tendency that more stochasticity leads to slightly elevated levels of genetic variation.

Thus, with a periodic optimum, additional stochasticity depletes genetic variation in the absence of mutation. But in the presence of mutation, even if of very low rate, it typically increases genetic variance. Therefore, mutation may 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 with stochasticity, the geometric mean fitness increases slower with L than without stochasticity (Figure 6b). The likely reason is that with much stochasticity, a population is often displaced from the optimum, even if otherwise it could track a deterministically cycling optimum.

To find out if our populations have reached approximate stationarity after 50,000 generations, for a subset of the parameters iterations were performed over 300,000 and 500,000 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, namely by down to $\frac{1}{3}$, for large fluctuations ($d = 1$). The reason is that absorption of alleles may 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 Figure 6a indicate. Clearly, this even 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 be 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 and Yampolsky (1996b), Korol et al. (1998), Bürger (1999) for the second, and to Bürger and Lynch (1995), Lande and Shannon (1996), Bürger (1999), and Bürger and Krall (2002) for the last topic.

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 behavior of gene frequencies is difficult to determine because several stable (periodic) equilibria, monomorphic and polymorphic, may coexist. Since 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 and 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 may be an important mechanism in maintaining genetic variation. They constructed numerous beautiful examples of multilocus systems in which stabilizing selection on a quantitative trait with a periodically changing optimum leads to various types of complex limiting behavior of the gene and gamete frequencies, sometimes chaotic like. 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 trait. Our aim was to go beyond special results by investigating a fairly large region of ecological parameters and, for each set of such parameters, obtaining numerical results of a large number of genetic systems. Our results show that, in the absence of mutation, 'on average' stabilizing selection with a periodic optimum never increases, actually 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 (for details, see The Statistical Approach), but the ecological parameters (strength of stabilizing selection, amplitude and period of the selection cycle, amount of stochasticity), as well as the number of loci and the mutation rate are fixed.

Among the genetic systems pertaining to such a parameter combination there may be large variation in the genetic variance maintained, and complex limiting behavior 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 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 behavior 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 mean fitness of their populations is generally very low, typically less than 10% of the maximum possible, often much less. For nonadditive loci, however, they observed complex limiting behavior under much weaker selection. Interestingly, in our investigation complex limiting behavior was mainly observed for periods longer than 24. However, the proportion of parameter sets showing such behavior 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 behavior, though 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. Therefore, we 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:

(i) 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 the period of the selection cycle is moderate or long (typically $L \geq 24$). For shorter periods and in the absence of stochasticity, only high per-locus mutation rates ($u > 10^{-4}$) have a notable effect.

(ii) Whereas in the absence of mutation, the genetic variance maintained decreases with increasing length L of the selection cycle, the opposite is true in the presence of mutation provided 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.

(iii) 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. Actually, for long periods ($L \geq 52$) 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.

(iv) 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 may be substantial.

Therefore, as argued previously for populations of finite size and traits determined by many loci (Kondrashov and Yampolsky 1996a,b, Bürger 1999) long-term fluctuations of the environment of this or similar kind may 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 directional selection in excess of about a dozen 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 in the presence of recurrent mutation and with moderate or long periods of the selection cycle, substantial genetic variation is maintained. 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 over a full selection cycle) be lower than the corresponding value of the heterozygote (Haldane and Jayakar 1963, Hoekstra 1975). If the fitness function is as in eqs. (1) and (2), this condition is, in fact, necessary and sufficient (Appendix A.2) and can be formulated as follows. Let the genotypic values at the locus under consideration be $\frac{1}{2} + h - a$, $\frac{1}{2} + h$, and $\frac{1}{2} + h + a$ ($a > 0$). Then a protected polymorphism exists if and only if $a > 2\,|h|$, i.e., the heterozygote must have its genotypic value closer to the midpoint $\frac{1}{2}$ of the selection cycle than any of the two homozygotes. Otherwise, the allele whose homozygous genotype is closer to $\frac{1}{2}$ 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 highest fitness during part of the selection cycle, so that this locus is not exclusively under directional selection, then with mutation and sufficiently long periods of the selection cycle substantial genetic variance can be maintained because recurrent mutation prevents allele frequencies of either type from becoming

extremely low during periods in which the other allele is selectively favored. 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 typically are displaced from the midpoint $\frac{1}{2}$, hence $|h| > 0$ in the above model. Therefore, there indeed is 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 less than two loci are maintained 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 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 (cf. Bürger and 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 may have already 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.

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A Appendix

For a trait determined by a single additive locus, subject to periodic stabilizing selection according to eqs. (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 two, three locally stable states can coexist: absorption of either of the two alleles and an interior limit cycle.

A.1 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 $t + kL$ ($t = 1, 2, \ldots, L$, $k = 1, 2, 3, \ldots$) are denoted by w_t, 1, v_t, respectively, and the relative frequency of allele A_1 by p. Then $p = 1$ (fixation of A_1) is a *linearly* stable equilibrium if and only if

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

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

$$P_v = \prod_{t=1}^{L} w_v > 1 \ . \tag{A.2}$$

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

$$\prod_{t=1}^{L} v_t < 1 \text{ and } \prod_{t=1}^{L} w_t < 1 \tag{A.3}$$

be 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, 1, v_1. (Note 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 local stability of $p = 1$. Applying the chain rule and using $g_i(1) = 1$ for all i, one obtains after some rearrangement (cf. Hoekstra 1975)

$$\left.\frac{d^2 f_L}{dp^2}\right|_{p=1} = 2P_w^{-2}\left[2(1 - P_w) + \sum_{j=1}^{L}(1 - v_j)\prod_{t=j}^{L} w_t\right] \ . \tag{A.4}$$

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

$$\sum_{j=1}^{L}(1 - v_j)\prod_{t=j}^{L} w_t > 0 \ . \tag{A.5}$$

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

A.2 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 $\frac{1}{2}$ of the selection cycle. Let the effects of the genotypic values of A_1A_1, A_1A_2, and A_2A_2 be $\frac{1}{2}+h-a$, $\frac{1}{2}+h$, and $\frac{1}{2}+h+a$, respectively, where $a>0$. Then the fitnesses of the three genotypes can be computed from eqs. (1) and (2). After normalizing the fitnesses of the heterozygote to 1 in each generation, we obtain

$$w_t = \exp[-as(a-2h)]\exp[-2asA\sin\frac{2\pi t}{L}]\,, \tag{A.6a}$$

$$v_t = \exp[-as(a+2h)]\exp[2asA\sin\frac{2\pi t}{L}]\,, \tag{A.6b}$$

and a further simple calculation yields

$$P_w = \exp[-asL(a-2h)]\,, \tag{A.7a}$$

$$P_v = \exp[-asL(a+2h)]\,. \tag{A.7b}$$

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

$$\begin{aligned}\sum_{j=1}^{L}(1-v_j)\prod_{t=j}^{L} w_t &= \sum_{j=1}^{L}\prod_{t=j}^{L} w_t - e^{-2a^2s}\sum_{j=1}^{L}\prod_{t=j+1}^{L} w_t \\ &= \left(1-e^{-2a^2s}\right)\sum_{j=1}^{L}\prod_{t=j}^{L} w_t + e^{-2a^2s}(P_w-1)\,.\end{aligned}$$

From (A.4), we can now infer that $\left.\frac{d^2 f_L}{dp^2}\right|_{p=1} > 0$ if $P_w = 1$ (actually, the same conclusion can be shown to be valid whenever $P_w < 1+\varepsilon$ for an appropriate $\varepsilon > 0$). Hence, in this model trajectories converging to the boundary $p=1$ ($p=0$) exist if and only if $P_w \geq 1$ ($P_v \geq 1$). Then the boundaries are also asymptotically stable.

Therefore, we can conclude the following:

(i) There exists a protected polymorphism if and only $a > 2\,|h|$, i.e., if and only if the value of the heterozygote is closer to $\frac{1}{2}$ 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.

(ii) If $h>0$ and $a \leq 2h$, then $p=1$ is locally stable and $p=0$ is unstable. Numerical computations of $f_L(p)$ suggests, that in this case $p=1$ is always globally stable, i.e., allele A_1 always becomes fixed.

(iii) If $h<0$ and $a \leq -2h$, then $p=0$ is locally stable and $p=1$ is unstable. Apparently, $p=0$ is globally stable.

A.3 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 satisfying $w_1 w_2 = 1$ 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

$$w_1 w_2 > 1 \quad \text{and} \quad \sum_{j=1}^{2}(1 - v_j)\prod_{t=j}^{2} w_t < 0 \tag{A.8}$$

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 $w_1 = 0.52$, $v_1 = 1.0$, $w_2 = 1.94$, and $v_2 = 1.1$ yields the desired numerical example, namely local stability of the boundaries $p = 0$ and $p = 1$, and local stability of the periodic equilibrium $\hat{p}(1) = 0.686$ and $\hat{p}(2) = 0.777$. If the initial fitnesses are w_1 and v_1, then every trajectory starting in the interval $(0, 0.308)$ converges to 0, every trajectory starting in $(0.934, 1)$ 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 $(0, 0.275)$ converge to 0, and those from $(0.886, 1)$ converge to 1. This can be proved straightforwardly by studying the numerator of $f_2(p)$ which is a polynomial of degree five. Since it has the two zeroes $p = 0$ and $p = 1$, the problem is reduced to analyzing a polynomial of degree three.

For cyclical selection with period $L \geq 3$, examples with more attractors should be constructable. 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 and Sigmund 1998, p. 241).