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FISHER'S GEOMETRICAL MODEL OF FITNESS LANDSCAPE AND VARIANCE IN FITNESS WITHIN A CHANGING ENVIRONMENT

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The fitness of an individual can be simply defined as the number of its offspring in the next generation. However, it is not well understood how selection on the phenotype determines fitness. In accordance with Fisher's fundamental theorem, fitness should have no or very little genetic variance, whereas empirical data suggest that is not the case. To bridge these knowledge gaps, we follow Fisher's geometrical model and assume that fitness is determined by multivariate stabilizing selection toward an optimum that may vary among generations. We assume random mating, free recombination, additive genes, and uncorrelated stabilizing selection and mutational effects on traits. In a constant environment, we find that genetic variance in fitness under mutation-selection balance is a U-shaped function of the number of traits (i.e., of the so-called "organismal complexity"). Because the variance can be high if the organism is of either low or high complexity, this suggests that complexity has little direct costs. Under a temporally varying optimum, genetic variance increases relative to a constant optimum and increasingly so when the mutation rate is small. Therefore, mutation and changing environment together can maintain high genetic variance. These results therefore lend support to Fisher's geometric model of a fitness landscape.

KEY WORDS: **Adaptation, changing environment, Fisher's geometrical model, genetic variance in fitness, mutation-selection balance, multivariate stabilizing selection.**

The fitness of an individual can be defined in terms of the number of its fertile offspring, and is a function of its survival and reproductive performance. Fitness can be regarded as a quantitative trait, but in natural populations it is difficult to determine how other traits influence fitness. Although it is clear that in *Drosophila*, for example, there is an overt relationship between female egg production and fitness, the relationship between bristle number and fitness is less obvious. For some traits there is likely to be a monotonic relationship with fitness, for others it may be quadratic with an intermediate optimum (Falconer and Mackay 1996; Walsh and Lynch 2009). How phenotype determines fitness is one of the fundamental challenges to developing the evolution theory of adaptation (Stearns and Hoekstra 2000; Orr 2005; Wagner and Zhang 2011).

Fisher's (1958) fundamental theorem shows that the rate of change in fitness is equal to the additive genetic variance in fitness. Thus natural selection would be expected to use up the useful variance (Crow 2008). However, variation in fitness remains at high levels in populations (Mousseau and Roff 1987; Merila and Sheldon 1999; Hill and Zhang 2008; Long et al. 2009).

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For example, Fowler et al. (1997) allowed replicated competition of a sample of wild-type third chromosome of *D. melanogaster* against balancer chromosomes in a population cage, and estimated fitness by recording changes in chromosome frequency. They obtained an estimate of the genetic variance in $\log_e$ fitness for the whole genome as high as 0.45. Genetic variation in fitness can be maintained by mutation and other factors such as heterozygote superiority and heterogeneous environments; genetic variation in other traits can remain through these factors and also because the covariance with fitness may be small (for discussion see, e.g., Falconer and Mackay 1996; Lynch and Walsh 1998; Bürger 2000; Zhang and Hill 2005a; Crow 2008). Although there are some theoretical models to provide qualitative understanding of why genetic variance in fitness remains (Charlesworth and Hughes 2000), satisfactorily quantitative models are not available. To understand the maintenance of genetic variance in fitness, we need a model to describe how fitness is controlled by mutant genes and genotypes and how natural selection acts on them.

Fisher (1930) was one of the first to consider this relationship. He introduced a geometrical model of natural selection acting on multiple quantitative traits that characterize an individual: each trait has an environment-dependent optimal value and the fitness of a complete phenotype is jointly determined by the distances of the traits from their optimal values. For phenotypes near this optimum, selection is of stabilizing type while phenotypes far from it are consequently subject to directional selection (Barton 1998). There is some evidence for stabilizing selection and consequent directional selection on various traits (Kingsolver et al. 2001; Elena and Lenski 2003; Hereford et al. 2004). Although this selection model appears simplistic, it has been widely applied to different aspects of evolutionary biology (e.g., Poon and Otto 2000; Orr 2000; Barton 2001; Welch and Waxman 2003; Waxman and Welch 2005; Martin and Gandon 2010). Importantly, an analysis of the fitness effects of mutations across environments shows that predictions from Fisher's geometrical model are consistent with empirical estimates, implying that multivariate stabilizing selection is a reasonable fitness landscape model (Martin and Lenormand 2006b).

A phenotype can be characterized by a very large number of traits (Zhang and Hill 2003; Wagner and Zhang 2011). Because the total number of genes is limited, most genes must affect more than one trait (i.e., pleiotropy is common) (Barton and Keightley 2002; Mackay 2004; Ostrowski et al. 2005; Weedon and Frayling 2008; Wagner et al. 2008; Wang et al. 2010). Further, environmental constraints on traits are not independent, so selection on these traits is also expected to be correlated (Welch and Waxman 2003; Zhang and Hill 2003; Blows 2007). The complicated situation can be reduced, however, by simultaneous diagonalization of the mutation matrix and the selection matrix (Zhang and Hill 2003; Hine and Blows 2006) such that the number of traits that are under independent selection and mutationally independent is much smaller (Waxman and Welch 2005; Hine and Blows 2006; McGuigan et al. 2011). By comparing theoretical predictions with empirical data on the distribution of mutational effects on fitness, Martin and Lenormand (2006a) suggest there could be less than three independent traits for some model species.

In the discussion of adaptation, it is usual to assume that the population has suffered a one time environmental change such that it departs from the current optimum for many generations (Orr 2005). The question of interest is how often the optimum changes and what kind of mutation emerges to help the population catch up with the changing optimum (Bello and Waxman 2006; Kopp and Hermisson 2007). A large change is rare but small changes must be frequent. The idea that an environmental change determines a new phenotypic optimum is supported by the long-term adaptation of experimental populations to new environments (for review see Elena and Lenski 2003 for microbes and Gilligan and Frankham 2003 for *Drosophila*). By comparing predictions for a fitness landscape model (Martin and Lenormand 2006a) and observations from mutation accumulation experiments, Martin and Lenormand (2006b) concluded that a Gaussian fitness function with a constant width across environments and with an environment-dependent optimum is consistent with the observed patterns of mutation accumulation experiments. As environment may change randomly or directionally, so does the movement in the optimum. With changes such as these in the position of the optimum, the effect of a mutant on fitness varies over generations even though the mutational effect on quantitative traits may not (Martin and Lenormand 2006b; cf. Hermisson and Wagner 2004).

Theoretical studies show that stabilizing selection toward a directionally moving optimum under recurrent mutation is an important mechanism for maintaining quantitative genetic variation (Bürger 1999; Waxman and Peck 1999; Bürger and Gimelfarb 2002). With a directionally moving optimum, mutant alleles suffer both stabilizing and directional selection; mutants become beneficial if they draw phenotypes toward the moving optimum and rise in frequency, which then increases the genetic variance. Previous investigations based on a quadratic fitness function, however, show that a randomly fluctuating optimum can hardly increase the quantitative genetic variance (Turelli 1988). Based on a Gaussian fitness function, Bürger and Gimelfarb (2002) showed that stochastic perturbation of a periodic optimum, in combination with recurrent mutation, can increase genetic variance substantially; but Bürger (1999) showed that purely fluctuating selection cannot increase genetic variance.

In this study we employ Fisher's (1958) model for the map between mutational effects on quantitative traits and the fitness effect with a changing optimum to investigate the variance in fitness under mutation-selection balance (MSB). Any realistic scenario

may be complicated, but here we consider an idealized situation of additive genes, free recombination, and a large population with random mating. Results from these simplified models should provide essential and useful information for more complicated and realistic situations. Moreover, taking into account empirical data for mutation and selection parameters, we test whether this model can provide a quantitative interpretation for the high level of genetic variance in fitness. Based on these results, we further discuss how pleiotropy affects the genetic variance in fitness and the so-called "cost of complexity" (Orr 2000), and review the validity of the Fisher geometric model of fitness.

Models

A population of N diploid monoecious individuals with discrete generations, random mating and at Hardy–Weinberg equilibrium, is assumed. The following independent and symmetric assumptions are made for mutational effects and selection on quantitative traits. Each individual is characterized by phenotypes of n independent identical quantitative traits $\boldsymbol{z} = (z_1, z_2, \ldots, z_n)^{\mathrm{T}}$ with T representing transposition. There is free recombination and additive gene action within and between loci. Mutations have effects $\boldsymbol{a} = (a_1, a_2, \ldots, a_n)^{\mathrm{T}}$ on the n traits, with a_i being the difference in value between homozygotes, with their density function $f(\mathbf{a})$ following a multivariate normal distribution $N(\mathbf{0}, \varepsilon^2\mathbf{I})$. A random-walk model of mutation is assumed (Crow and Kimura 1963; Zeng and Cockerham 1993): a mutation of effect $\boldsymbol{a}$ changes the phenotype of an individual from $\boldsymbol{z}$ to $\boldsymbol{z} + \boldsymbol{a}$. Here we implicitly assume the so-called Euclidean superposition model, within which mutational effects on individual traits are independent of the total number of traits affected and have the same mean (Wagner et al. 2008).

We assume there is no genotype-environment interaction and the environmental variation in a quantitative trait is $N(0, V_{\mathrm{E}})$. Thus, by averaging environmental deviations, the phenotype $\boldsymbol{z}$ is simply represented by its genotype (Turelli 1984). Individuals are subject to real stabilizing selection, with independent and identical strength of selection on each trait, characterized by $\mathbf{S} = \zeta^2\mathbf{I}$, where $\zeta^2 = 1/(2V_{\mathrm{S}})$ and V_{S} is the variance of the fitness profile on each trait. Multivariate Gaussian fitness

$$W(\mathbf{z}) \equiv \exp(Q) = \exp\left[-\frac{1}{2}\sum_{j=1}^{n}(z_j - o_j)^2\zeta_j^2\right] \qquad (1)$$

is assigned to genotypic values $\boldsymbol{z}$, with the optimum phenotype $\boldsymbol{o} = (o_1, o_2, \ldots, o_n)^{\mathrm{T}}$, and the $\log_e$ fitness is defined as

$$Q \equiv \ln(W(z)) = -\frac{1}{2}\sum_{j=1}^{n}(z_j - o_j)^2\zeta_j^2. \qquad (2)$$

We consider the following schemes for a moving optimum.

(1) *Directionally moving optimum*: The optimum, starting from **0,** moves at a constant rate $\boldsymbol{\kappa} = (\kappa, \kappa, \ldots, \kappa)$,

$$\boldsymbol{O}_t = \boldsymbol{\kappa} t, \qquad (3)$$

(cf. Charlesworth 1993; Bürger 1999; Waxman and Peck 1999). We employ the standard deviation of environmental variation in trait (i.e., $\sigma_{\mathrm{E}} = \sqrt{V_{\mathrm{E}}}$) as a suitable scale (cf. Houle 1992).

(2) *Gaussian change* (i.e., white noise): We assume optimal values are independent and identical and the optimum for each trait fluctuates around its overall mean zero with variance V_{O}. The optimum phenotype $\boldsymbol{o}_t$ among traits within generation is distributed as $N(\mathbf{0}, V_{\mathrm{O}}\mathbf{I})$.

(3) *Markov process*: A simple situation where optimal values for different traits are uncorrelated, but those for the same trait are autocorrelated among generations. The optimum follows a linear stationary Markov process, with mean zero, variance $V_{\mathrm{O},j}$, and autocorrelation coefficient d_j ($-1 < d_j < 1$) between $o_{t,j}$, $t = 0, 1, 2, \ldots$. for trait j; that is,

$$O_{j,t} = d_j O_{j,t-1} + \delta_{j,t-1}, \quad j = 1, \ldots, n \qquad (4)$$

(Charlesworth 1993). Here δ_j represent white noise with mean zero and variance V_j, with $V_{\mathrm{O},j} = V_j/(1 - d_j)^2$. Only the symmetric situation is considered, where $V_j = V$ and $d_j = d, j = 1, \ldots, n$.

(4) *Periodically moving optimum*: To take into account autocorrelation among optimal values, we consider they change in a periodic way as

$$O_{j,t} = A\sin(2\pi t/P), \quad j = 1, \ldots, n \qquad (5)$$

with a period of P generations and an amplitude A (cf. Charlesworth 1993; Bürger and Gimelfarb 2002). The optimum will have mean zero and variance $A_j^2/2$ for trait j. It changes more regularly than the randomly changing optimum but less so than the directionally moving optimum.

Methods

We use Monte-Carlo simulations to investigate genetic variances in quantitative traits and in fitness. For constant and randomly varying environments, results are also obtained by employing Kimura's (1969) diffusion approximation.

DIFFUSION APPROXIMATION

Let the frequencies of the wild-type allele (A) and the mutant allele (a) at locus i be $1 - x_i$ and x_i, respectively, the frequencies of genotypes AA, Aa, and aa assuming Hardy–Weinberg proportions are $(1 - x_i)^2$, $2x_i(1 - x_i)$, and ${x_i}^2$. With additive gene action, the

genotypic values for the quantitative trait j are 0, $\frac{1}{2}a_{i,j}$, and $a_{i,j}$. Summing over all loci, the genetic variance in quantitative trait j can be written as

$$V_{G,j}(\mathrm{T}) = \sum_i H(s_i)a_{i,j}^2/4 \quad j = 1, \ldots, n. \tag{6}$$

Here $H(s_i) = 2x_i(1 - x_i)$ is the heterozygosity at locus i and the frequency x_i is determined by the selective value $s_i \equiv \mathrm{W}(z+\mathbf{a}_i)/\mathrm{W}(z) - 1$ for the mutation with effects $\mathbf{a}_i$. With a fixed optimum, the mean phenotype is coincident with the optimum (Bürger 2000) and the selective value of mutant allele i can be approximated by

$$s_i \approx Q_i = -\frac{1}{2}\sum_{j=1}^{n} a_{i,j}^2\zeta^2 \tag{7}$$

(Zhang and Hill 2003). Here, Q_i is the value of $\log_e$ fitness due to the mutant at locus i and is approximately equal to s_i when s_i is small.

Using Kimura's (1969) diffusion approximation for heterozygosity $H(s_i)$ at MSB, the genetic variance in a quantitative trait can be obtained via integration over mutational effects across the whole genome (see (A10)). Although mutational effects on quantitative traits are assumed to be additive, their selective values are not because, as Martin et al. (2007) pointed out, there is pervasive complicated interaction among mutants for fitness in the Fisher model. Therefore, the genetic variance in fitness cannot be expressed simply in terms of heterozygosity (Falconer and Mackay 1996), but in terms of mutational effects on traits (see Appendix A).

Within a changing environment, the mean phenotype will differ from the current optimum and the selective value of the mutation at generation t is dependent on this difference and approximated by

$$s_{i,t} \approx Q_{i,t} = -\zeta^2\sum_{j=1}^{n}\left[\frac{1}{2}a_{i,j}^2 - (o_{j,t} - z_{j,t})^2 a_{i,j}^2\zeta^2 - (o_{j,t} - z_{j,t})\,a_{i,j}\right] \tag{8}$$

(cf. Zhang and Hill 2005b; Appendix A). If the optimum changes randomly and slowly around its mean so that fluctuations in $s_{i,t}$ remain small and the population stays near MSB, the mean selective value over generations is approximately

$$\hat{s}_i \approx \hat{Q}_i = -\zeta^2\sum_{j=1}^{n}\left[\frac{1}{2}a_{i,j}^2(1 - 2V_O\zeta^2)\right], \tag{9}$$

and the heterozygosity can be approximated as for constant environments by using the mean selective value. Derivations of $V_G(\mathrm{T})$ and $V_G(\mathrm{F})$ for constant and randomly varying environments are given in Appendices A and B, respectively.

INDIVIDUAL-BASED MONTE-CARLO SIMULATIONS

A multiple-locus and individual-based simulation procedure, modified from Zhang and Hill (2003), is used to explore the situation when the optimum moves among generations. The population is started from an isogenic state and allowed to proceed $4N$ generations to reach equilibrium. The genome is assumed to comprise L loci and the phenotype $\boldsymbol{z}$ is determined by the $2L$ alleles as $z_j = \sum_{i=1}^{2L} y_{i,j}$, where $y_{i,j}$ is the effect of allele i on trait j and the corresponding fitness is given by a Gaussian fitness function (1).

Each generation, the sequence of operations is mutation, selection, mating and recombination, and reproduction. The haploid genome wide mutation rate is $\lambda = \sum_{i=1}^{L} u_i$, where u_i is the rate of mutation at locus i. The mutant effect $\boldsymbol{a}$ is sampled from $N(\mathbf{0}, \varepsilon^2\mathbf{I})$ as described above. A large population size N is chosen to ensure strong selection. The relative fitness of individual l is assigned as $w_{l,t} = W_{l,t}/W_{\mathrm{Max},t}$ so that $0 \le w_{l,t} \le 1, l = 1, \ldots, N$, where $W_{\mathrm{Max},t}$ is the maximum fitness at generation t. The chance that individual l is chosen as a parent of generation $t+1$ is proportional to $w_{l,t}$. The steady system is run for τ ($= 3000$) generations, and within each generation the mean and variance of fitness are calculated as

$$\overline{w}_t = \frac{1}{N}\sum_{l=1}^{N} w_{l,t} \quad \text{and} \quad Var(w_t) = \frac{1}{N-1}\sum_{l=1}^{N}(w_{l,t} - \overline{w}_t)^2.$$

The average variance within generations

$$V_G(\mathrm{F}) = \frac{1}{\tau}\sum_{t=1}^{\tau} Var(w_t) \approx \frac{1}{N\tau}\sum_{t=1}^{\tau}\sum_{l=1}^{N}(w_{l,t} - \overline{w}_t)^2, \tag{10}$$

and the average mean fitness,

$$E(\mathrm{F}) = \frac{1}{\tau}\sum_{t=1}^{\tau}\overline{w}_t = \frac{1}{N\tau}\sum_{t=1}^{\tau}\sum_{l=1}^{N} w_{l,t} \tag{11}$$

are calculated, together with the corresponding quantities for $\log_e$ fitness and the quantitative traits.

The standardized quadratic selection gradient (i.e., the regression of fitness on squared deviation of trait value from the mean) is used to measure the strength of apparent stabilizing selection on each trait (Keightley and Hill 1990; Johnson and Barton 2005). Trait j is assumed to be under real stabilizing selection with an intrinsic strength ${\zeta_j}^2 = 1/(2V_{S,j})$, where $V_{S,j}$ denotes the variance of the fitness function of real stabilizing selection against trait j. The apparent stabilizing selection on trait j is due to the pleiotropic effect and its observed strength (denoted by $\zeta_{ST,j}^2$) is an outcome of real stabilizing selection on all traits. To calculate $\zeta_{ST,j}^2$, the covariance between fitness and squared deviation of phenotypic value from its mean and the variance of the squared

deviation at generation t are computed as

$$\mathrm{cov}(w_t, (z_{j,t} - \bar{z}_{j,t})^2) = \frac{1}{N}\sum_l w_{l,t}(z_{l,j,t} - \bar{z}_{j,t})^2 - \frac{1}{N}\sum_l w_{l,t} \times \frac{1}{N}\sum_l (z_{l,j,t} - \bar{z}_{j,t})^2$$

$$V_{\mathrm{G2},j,t} = \frac{1}{N}\sum_l (z_{l,j,t} - \bar{z}_{j,t})^4 - \left[\frac{1}{N}\sum_l (z_{l,j,t} - \bar{z}_{j,t})^2\right]^2.$$

Taking the average of the regression coefficients $b_{j,t} = \mathrm{cov}(w_t, (z_{j,t} - \bar{z}_t)^2)/V_{\mathrm{G2},j,t}$ over τ generations, the strength of apparent stabilizing selection on a quantitative trait is approximated by

$$\zeta^2_{\mathrm{ST},j} \equiv 1/(2V_{\mathrm{ST},j}) = -\frac{1}{\tau}\sum_t b_{j,t} \tag{12}$$

(Keightley and Hill 1990). Here, $V_{\mathrm{ST},j}$ is defined equivalently as the variance of the fitness function of apparent stabilizing selection against quantitative trait j, and is referred to subsequently as the inverse of the strength of apparent stabilizing selection.

Results

UNCHANGED ENVIRONMENT

For the situation where the optimum is constant and the n quantitative traits are independent in both mutational effects and selection, an expression for the quantitative genetic variance $V_{\mathrm{G},j}(\mathrm{T})$, $j = 1, \ldots, n$, was given by Zhang and Hill (2003) for some special cases. Under weak mutation strong selection (WMSS), the genetic variance in fitness under MSB is

$$V_{\mathrm{G}}(\mathrm{F}) = \sum_{j=1}^{n} \zeta_j^2[V_{\mathrm{M},j} + 2(V_{\mathrm{G},j}(\mathrm{T})\zeta_j)^2] \tag{13}$$

(see Appendix A), where $V_{\mathrm{M},j} = \lambda\varepsilon_i{}^2/2$ is the mutational variance on quantitative trait j. Intuitively this can be understood as follows. Variance in fitness, as in (A4), is determined by the sum of the fourth moments of mutational effects on quantitative traits, in which the two-fold action of selection can be decomposed into two parts (see (A5)). The first is the sum of products of squared effects of mutations on the traits and the second is the sum of squares of their genetic variance–covariances. The first part can be further arranged into a product of the sum of squared effects (see (A12)). Under WMSS, the heterozygosity is approximated by (A8) with the selective value s given by (7). One sum of squared effects in the first part is then cancelled out with that in s, and another sum of squared effects makes the sum of V_{M}. With one-fold action of selection, they make the first part in (13). The reasoning is similar to the House-of-Cards approximation for $V_{\mathrm{G}}(\mathrm{T})$ under MSB (Turelli 1984; Bürger 2000). Mutational variances contribute linearly to $V_{\mathrm{G}}(\mathrm{F})$ and differ from the contributions from standing genetic variances in traits.

The mean fitness can be approximated as follows. By definition, $E(\mathrm{F}) = \prod_i [1 - 2(1 - x_i)x_i h_i s_i - x_i^2 s_i] \approx 1 - \sum_i (2(1 - x_i)x_i h_i s_i + x_i^2 s_i)$, where h_i is the dominance coefficient of the mutant effect on the quantitative trait at locus i. Under WMSS, the frequency x_i is very low and approximated by $x_i \approx u_i/(h_i s_i)$; then

$$E(\mathrm{F}) \approx 1 - \sum_i 2x_i h_i s_i \approx 1 - \sum_i 2u_i = 1 - 2\lambda. \tag{14}$$

Here 2λ is the mutational load (Haldane 1932). Note that $E(\mathrm{F})$ is determined only by the mutation rate and is independent of the number of traits (cf. Poon and Otto 2000).

Under the independent and symmetric situation assumed in this study, the genetic variances in quantitative traits and in fitness can be expressed as,

$$V_{\mathrm{G},j} = V_{\mathrm{G}}(\mathrm{T}) = 4\lambda V_{\mathrm{S}}/n, \quad j = 1, \ldots, n, \tag{15}$$

$$V_{\mathrm{G}}(\mathrm{F}) = \frac{nV_{\mathrm{M}}}{2V_{\mathrm{S}}} + \frac{8\lambda^2}{n}, \tag{16}$$

respectively (see Appendix A). Here $V_{\mathrm{G}}(\mathrm{T})$ represents genetic variance in any identical independent trait. The genetic variance in fitness $V_{\mathrm{G}}(\mathrm{F})$ comprises two parts, the first is proportional to the mutational variance in quantitative traits and the second to the square of the genomic mutation rate. With an increasing number of traits the first part increases and the second decreases. Therefore, the first part becomes important if the number of traits is large and the second if few independent traits are under selection, so $V_{\mathrm{G}}(\mathrm{F})$ is a U-shaped function of the number of traits (Fig. 1C). The expression for the inverse of the strength of apparent stabilizing selection under multivariate quadratic stabilizing selection was given by Zhang and Hill (2003)

$$V_{\mathrm{ST}} = V_{\mathrm{S}}\frac{16V_{\mathrm{S}}\lambda^2 + 3n^2V_{\mathrm{M}}/(n+2)}{16V_{\mathrm{S}}\lambda^2 + n^2V_{\mathrm{M}}}. \tag{17}$$

The theoretical approximations are in good agreement with simulations (Fig. 1). When selection is sufficiently weak, both Gaussian and quadratic stabilizing selection should be roughly the same. This is confirmed by simulations when mutation rate is low (i.e., $\lambda < 0.1$). The difference between Gaussian and quadratic fitness functions emerges with increasing mutation rate. When $\lambda = 0.1$, the apparent stabilizing selection under Gaussian stabilizing selection is noticeably weaker than that under quadratic stabilizing selection (i.e., V_{ST} is larger, see Fig. 1D) and consequently $V_{\mathrm{G}}(\mathrm{T})$ is higher (Fig. 1B) but $V_{\mathrm{G}}(\mathrm{F})$ lower (Fig. 1C). The agreement between simulations and approximations degenerates with a high mutation rate (Fig. 1A–C), or if the strength of real stabilizing selection is reduced from 0.1 to 0.025 (i.e., V_{S}

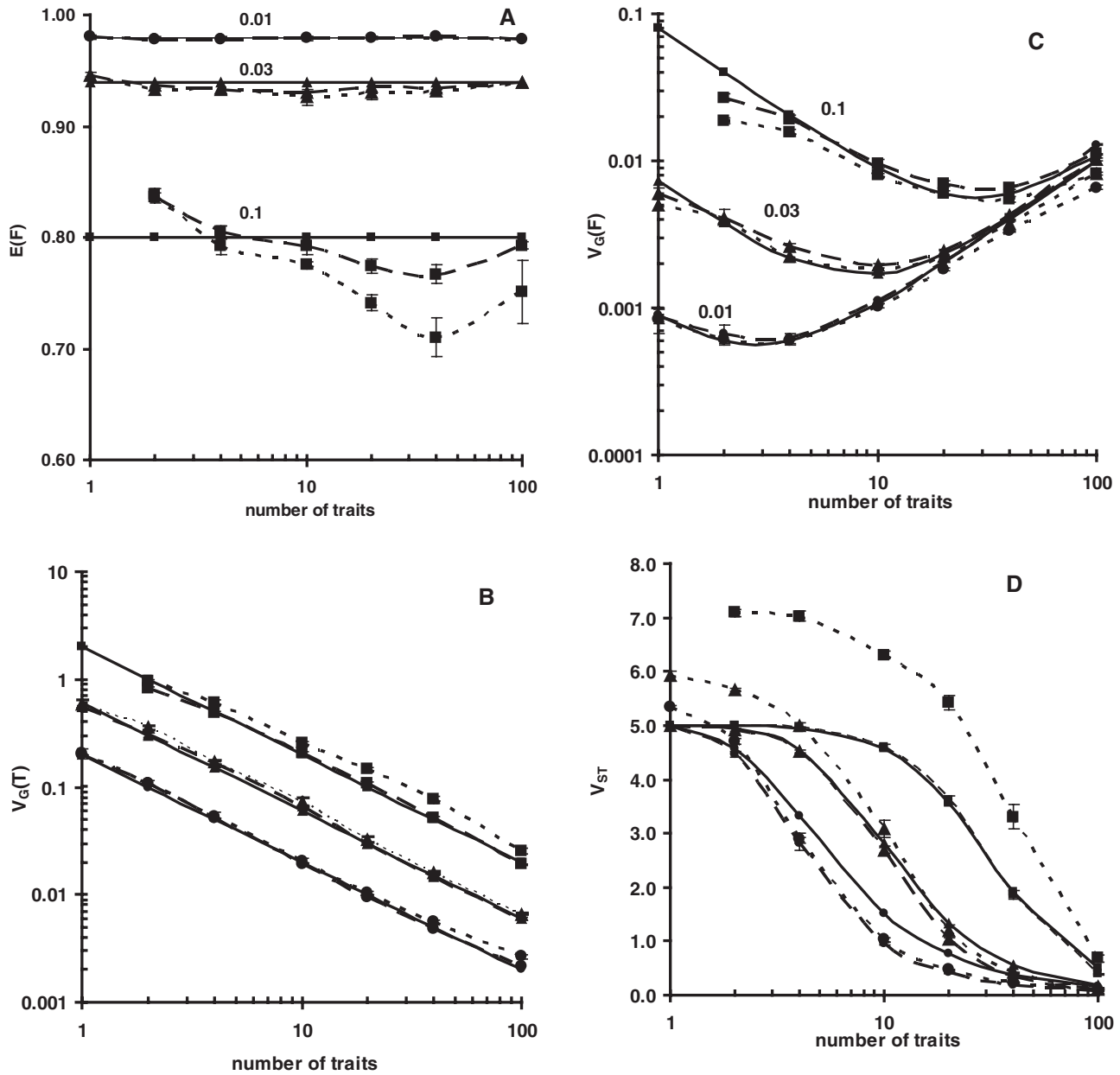

Figure 1. **Comparison between Monte-Carlo simulations and diffusion approximations of (A) mean fitness under the constant optimum, (B) genetic variance in quantitative trait, (C) genetic variance in fitness, and (D) the inverse of the strength of apparent stabilizing selection (V_{ST}). The diffusion approximations (solid lines) for E(F), V_G(T), V_G(F), and V_{ST} are from equations (14)–(17). The simulation results are obtained for a population of size $N = 1000$ under real stabilizing selection of both quadratic (dashed lines) and Gaussian fitness (dotted lines) function with $V_S = 5V_E$. The mutational variance in each quantitative trait is $V_M = 10^{-3}V_E$ per generation, and there are $L = 3000$ loci within the genome. Mutation rates $\lambda = 0.01$, 0.03, and 0.1 per haploid genome per generation represented by circles, triangles, and squares, respectively. The error bars stand for standard deviations.**

increased from $5V_E$ to $20V_E$) even $\lambda = 0.03$ (data not shown). This indicates that these theoretical approximations hold only under WMSS (i.e., a low $\lambda V_S/V_M$ approximation) (cf. Bürger 2000).

Estimates from empirical data indicate that the mutational variance in quantitative traits (V_M) over many traits and species is centered around $10^{-3}V_E$ with a range 10^{-5}–$10^{-2}V_E$, where V_E is the environmental variance (Falconer and Mackay 1996; Houle et al. 1996; Lynch and Walsh 1998; Keightley 2004; Keightley and Halligan 2009). Estimates of the genome wide mutation rate λ cover a wide range for multicelluar enkaryotes. For example, those for *Caenorhabditis elegans*, *Drosophila,* and mouse are 0.036, 0.14, and 0.9 per haploid genome per generation, respectively (Drake et al. 1998). The width of stabilizing selection on a single

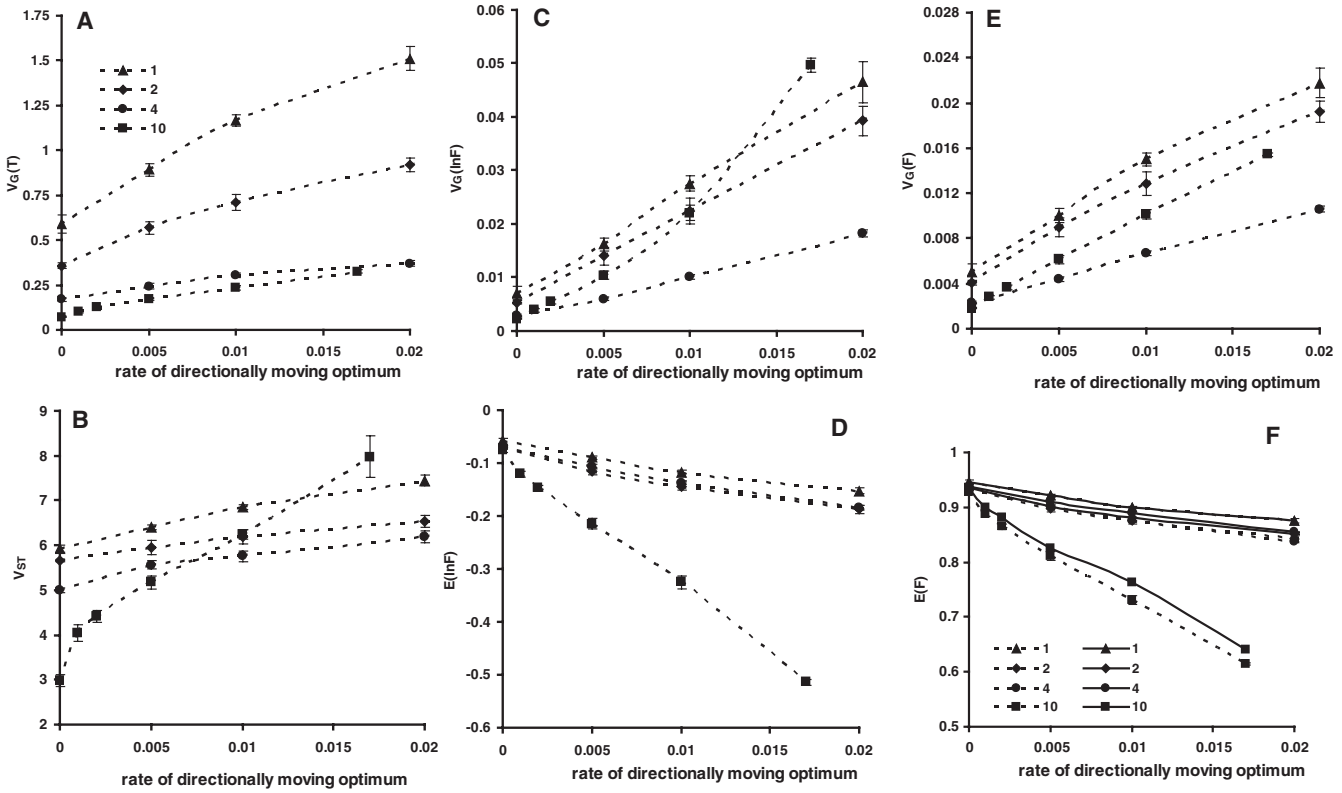

Figure 2. **The influence of a directionally moving optimum on (A) genetic variance in a quantitative trait, (B) the inverse of the strength of apparent stabilizing selection on a quantitative trait (V_{ST}), (C) genetic variance in $\log_e$ fitness, (D) average of $\log_e$ fitness, (E) genetic variance in fitness, and (F) average of fitness. Results were obtained by simulations. The solid lines in panel (F) are predictions from (20), where the values of $V_G(T)$ in panel (A) were used. Model parameters: population size $N = 1000$, genomic mutation rate $\lambda = 0.03$ per generation, the number of loci $L = 3000$, mutational variance $V_M = 10^{-3}V_E$ per generation. The n identical independent traits are assumed to be under real stabilizing selection with a Gaussian fitness function with intrinsic strength $\zeta^2 = 1/(2V_S) = 0.1$ on each trait and moving optimum: $\Theta_i(t) = kt$, $i = 1, \ldots, n$. The averages are obtained over 3000 generations at equilibrium. The error bars stand for standard deviations. $n = 1$, 2, 4, and 10 traits are illustrated.**

quantitative trait (V_S) has been estimated as typically in the range 5–20V_E (Turelli 1984; Endler 1986; Falconer and Mackay 1996; Kingsolver et al. 2001). Assuming these typical estimates, genetic variance in relative fitness above 0.002 can be maintained only when λ exceeds 0.3 and the number of traits is small (i.e., $n < 10$) (see Fig. 1B). If λ is low and n is large but less than 1000, however, only a very low $V_G(F)$ is maintained (Fig. 1B).

CHANGING ENVIRONMENT

To focus on the impact of a changing optimum on genetic variance, we consider only the independent and symmetric situation where all traits are under stabilizing selection of the same strength $\zeta_j^2 = 1/(2V_S)$, $j = 1, \ldots, n$, have the same mutational variance $V_{M,j} = V_M$, and have independent and equivalent optimal values.

DIRECTIONALLY MOVING OPTIMUM

Under a directionally moving optimum, the mean phenotype in the population responds to it with a delay (Bürger 1999; Waxman and Peck 1999),

$$\bar{z}_{j,t} - o_{j,t} \equiv \Delta = -\kappa \frac{V_S + V_G(T)}{V_G(T)}, \quad j = 1, \ldots, n. \quad (18)$$

Equation (18), confirmed by simulations (data not shown), can be derived directly from the standard selection equation (Bulmer 1985 p. 151; cf. Charlesworth 1993; Bürger and Lynch 1995). Applying (18) to (8), the selective value of the mutant allele at locus i is approximately

$$s_i \approx Q_i = -\zeta^2 \sum_{j=1}^{n} \left[\frac{1}{2} a_{i,j}^2 (1 - 2\Delta^2 \zeta^2) - a_{i,j}\Delta \right]. \quad (19)$$

It is obvious that mutant alleles are also under directional selection: those that bring the mean phenotype closer to the optimum will be at a selective advantage and increase in frequency. Further, the apparent stabilizing selection on each trait is reduced (Fig. 2B; Table S1). Therefore, $V_G(T)$ increases even though mutational effects on traits remain unchanged (Fig. 2A; Table S1; cf. Bürger 1999; Waxman and Peck 1999). $V_G(F)$ also increases because

beneficial effects increase as the lag Δ increases, as suggested by (19) (Fig. 2E; Table S1). The mean fitness reduces (Fig. 2F), however, and when the rate κ is small, can be approximated as

$$E[F] = \sqrt{\frac{V_S}{V_S + nV_G(T)}} \exp\left\{\frac{-n\Delta^2}{2[V_S + nV_G(T)]}\right\}. \quad (20)$$

Equation (20) can also be obtained directly as for (18) (Bulmer 1985; cf. Charlesworth 1993). In terms of the impact of a changing environment on adaptation, the results indicate that, even though it reduces mean fitness, it facilitates the survival of a population by increasing its variance in fitness (Gomulkiewicz and Holt 1995).

The increases in genetic variance due to a changing relative to a constant optimum depend on the number of traits and the mutation rate. For example, with a rate of movement $\kappa = 0.02\sigma_E$ per generation and mutation rate $\lambda = 0.03$, the relative increase in $V_G(T)$ is 2.6- and 5.3-fold, in $V_G(F)$ is 4.3- and 10-fold, and in $V_G(\ln F)$ is 6.6- and 26-fold for $n = 1$ and 10 traits, respectively. For four traits and a rate of $\kappa = 0.02\sigma_E$, the relative increase in $V_G(T)$ is 1.5- and 11-fold, in $V_G(F)$ 1.8- and 21-fold, and in $V_G(\ln F)$ 2.5- and 32-fold for $\lambda = 0.1$ and 0.005, respectively (cf. Waxman and Peck 1999; Table S1). Therefore, although the genetic variances are small for low mutation rates and many traits with a constant optimum, directional changing optimum can boost them to large values (Fig. 1 and Table 1).

Table 1. Comparison among four types of environmental change on the genetic variance in quantitative traits $V_G(T)$, fitness $V_G(F)$, and $\log_e$ fitness $V_G(\ln F)$. Model parameters: $\lambda = 0.03$, $V_S = 5V_E$, $N = 1000$, and $L = 3000$. The linear regression coefficient of increase in variance versus the loss of fitness is used to characterize the increase of variance among different types of environmental change. This estimate is obtained by using only the results from the situations of a weakly changing optimum. The values listed here are from analysis of Figures 2, 4–6.

Types of environmental change	Number of traits (n)	Increase in variance per unit of fitness loss		
		$V_G(T)$	$V_G(F)$	$V_G(\ln F)$
Directionally moving optimum	1	13	0.22	1.6
	4	2.3	0.077	0.56
	10	0.87	0.031	0.14
Randomly moving optimum	1	2.4	0.17	0.34
	4	0.29	0.050	0.083
	10	0.031	0.0049	0.012
Optimum following a linear stationary Markov process	1	2.2	0.16	0.62
	4	0.76	0.027	0.29
	10	0.59	0.0074	0.39
Periodically changing optimum	1	3.2	0.17	1.2
	4	0.33	0.043	0.11
	10	0.12	0.013	0.080

RANDOMLY VARYING OPTIMUM

The population mean phenotype responds to the optimum, but remains behind the mean of the optimum over generations. As an example, the standard deviation of trait mean between generations is only $0.2\sigma_E$ when that of the optimum over generations is $\sqrt{V_O} = 2.0\sigma_E$ (Fig. 3).

Influence of a randomly varying optimum on genetic variances in quantitative traits and fitness is shown in Figure 4. Under Gaussian stabilizing selection, $V_G(T)$ increases with V_O; when the variance in the optimum is small (e.g., $V_O << V_S$),

$$V_G(T) = \frac{4\lambda V_S}{n(1 - V_O/V_S)} \quad (21)$$

(Fig. 4A; Appendix B). The underlying reason for this increase is that the actual strength of stabilizing selection weakens (Fig. 4B). Approximation (21) holds only under restrictive conditions because it was obtained under quadratic stabilizing selection (Appendix B). To compare it with simulation results under Gaussian stabilizing selection the apparent stabilizing selection must be weak so both have approximately similar effect. If overall stabilizing selection is strong, Gaussian becomes much weaker than quadratic stabilizing selection and hence (21) underpredicts simulation results for $V_G(T)$ (see Fig. 4A for $n = 10$). However, if it is too weak, Kimura's (1969) diffusion approximation for

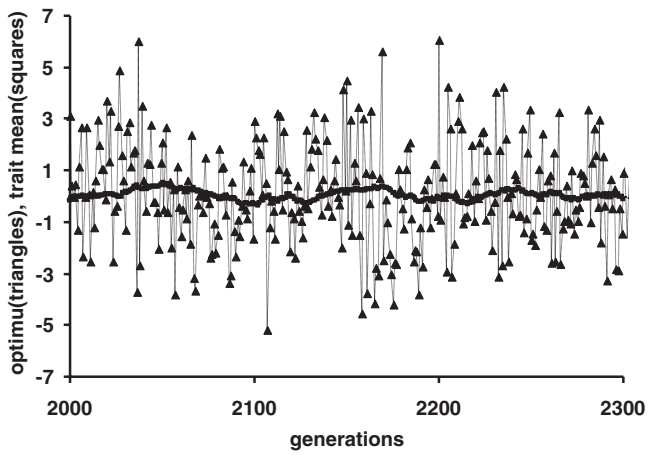

Figure 3. The change of trait mean under a randomly varying optimum. A population of size $N = 500$ is started from an isogenic state and is allowed $4N$ generations to reach equilibrium. The phenotypic mean and the optimum for trait 1 are recorded each generation. With a large standard deviation, $2.0\sigma_E$, in the optimum, the standard deviation of phenotypic mean among generations is only about $0.2\sigma_E$. Model parameters: $\lambda = 0.05$ per haploid genome per generation, four identical independent traits under real stabilizing selection with a Gaussian fitness function with $V_S = 5V_E$.

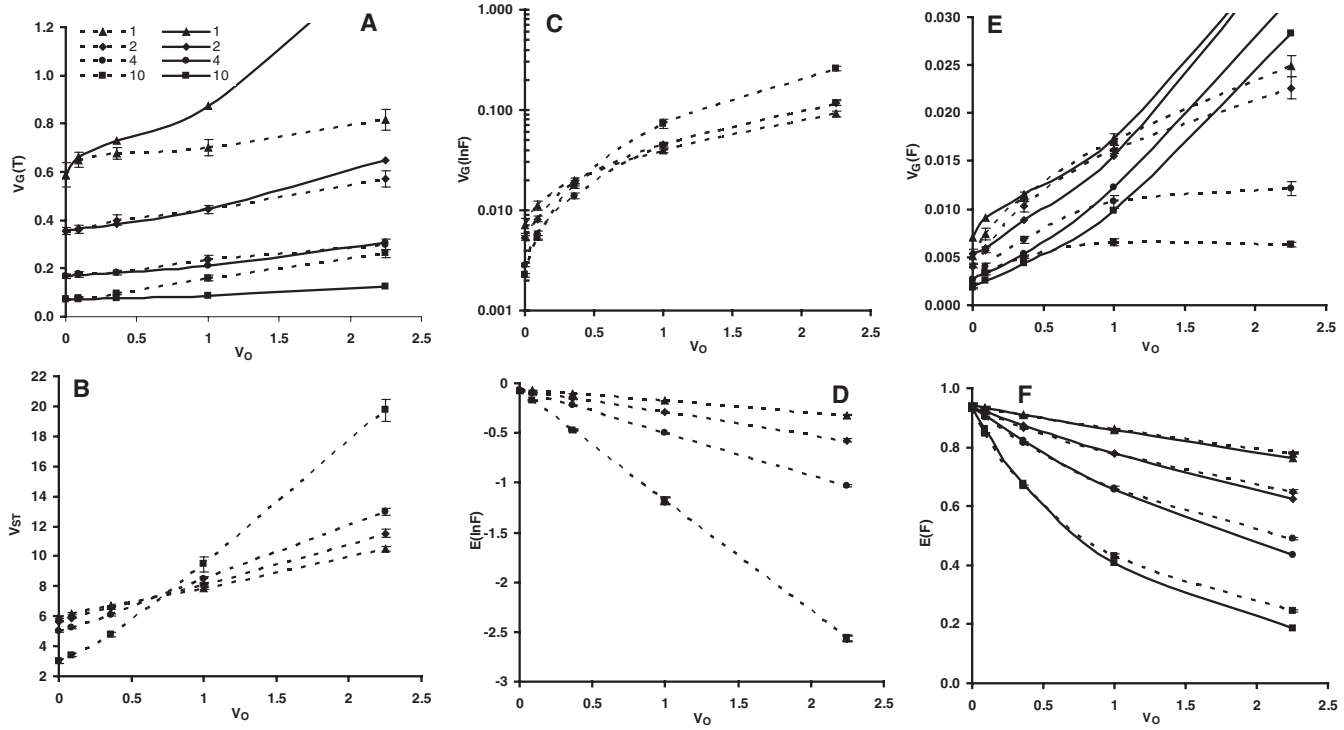

Figure 4. **Impact of a randomly varying optimum on (A) genetic variance in a quantitative trait, (B) the inverse of the strength of apparent stabilizing selection on a quantitative trait (V_{ST}), (C) genetic variance in $\log_e$ fitness, (D) average of $\log_e$ fitness, (E) genetic variance in fitness, and (F) average of fitness. Model and simulation otherwise are as Figure 2. Results represented by dashed lines are from simulations where the solid lines in panels (A), (E), and (F) represent theoretical approximations from equations (21), (22), and (24), respectively. n = 1, 2, 4, and 10 traits are illustrated.**

heterozygosity under strong selection (i.e., $2N|s| >> 1$) breaks down because mutations accumulate and linkage disequilibrium and other complications reduce the genetic variance (Zhang and Hill 2003). For one trait situation under weak overall stabilizing selection, the prediction (21) exceeds simulation results. Furthermore, both the mutation rate and the magnitude of fluctuation in optimum cannot be large, but for $\lambda < 0.1$ and $V_O < 0.4V_E$, (21) agrees qualitatively with simulation results (Fig. 4A; Table S2).

The genetic variances in fitness and in $\log_e$ fitness also increase with V_O (Fig. 4C and E). This can be understood as follows. As V_O increases, the average selective value decreases (see (9)), mutant alleles become less deleterious, and their frequencies and heterozygosity increase. Further, $V_G(F)$ is proportional to the mean square of fitness effects, which increase under a randomly changing optimum (see (B4)). The two factors work together to increase $V_G(F)$. When the variance in the optimum is small ($V_O << V_S$),

$$V_G(F) = \frac{nV_M}{2V_S}(1 - V_O/V_S) + \frac{8\lambda^2}{n(1 - V_O/V_S)^2} + \frac{\lambda V_O}{V_S(1 - V_O/V_S)} \quad (22)$$

(Fig. 4E; Appendix B). Compared with predictions for $V_G(F)$ in a constant environment (16), there is an extra item in (22), $\lambda V_O/(V_S - V_O)$, roughly proportional to λV_O. Because $V_G(F)$ is an integrative measure of variance in multiple traits, approximation (22) holds under even more restrictive conditions than (21) (Appendix B). Therefore, its fit to numerical simulations becomes less satisfactory although providing an adequate qualitative description (Fig. 4E; Table S2).

As V_O increases, the mean square difference between the population mean and the optimum of a quantitative trait also increases as

$$E((\bar{z} - o)^2) = 2V_O\left(\frac{V_G(T) + V_S}{V_G(T) + 2V_S}\right) \quad (23)$$

(Charlesworth 1993; see Fig. 4B), showing that it roughly equals V_O when $V_G(T) << V_S$. The mean fitness decreases with V_O as

$$E[F] = \sqrt{\frac{V_S}{V_S + nV_G(T)}}\exp\left(-\frac{nV_O}{2[V_S + nV_G(T)]}\right) \quad (24)$$

(Charlesworth 1993). The simulations agree well with this approximation (Fig. 4F).

With a randomly changing optimum, the genetic variance in fitness can increase to substantial levels. For a constant optimum as in Table S2 where four traits are assumed, $V_G(F) = 0.016$ when $\lambda = 0.1$, and increases two-fold, to $V_G(F) = 0.031$, when

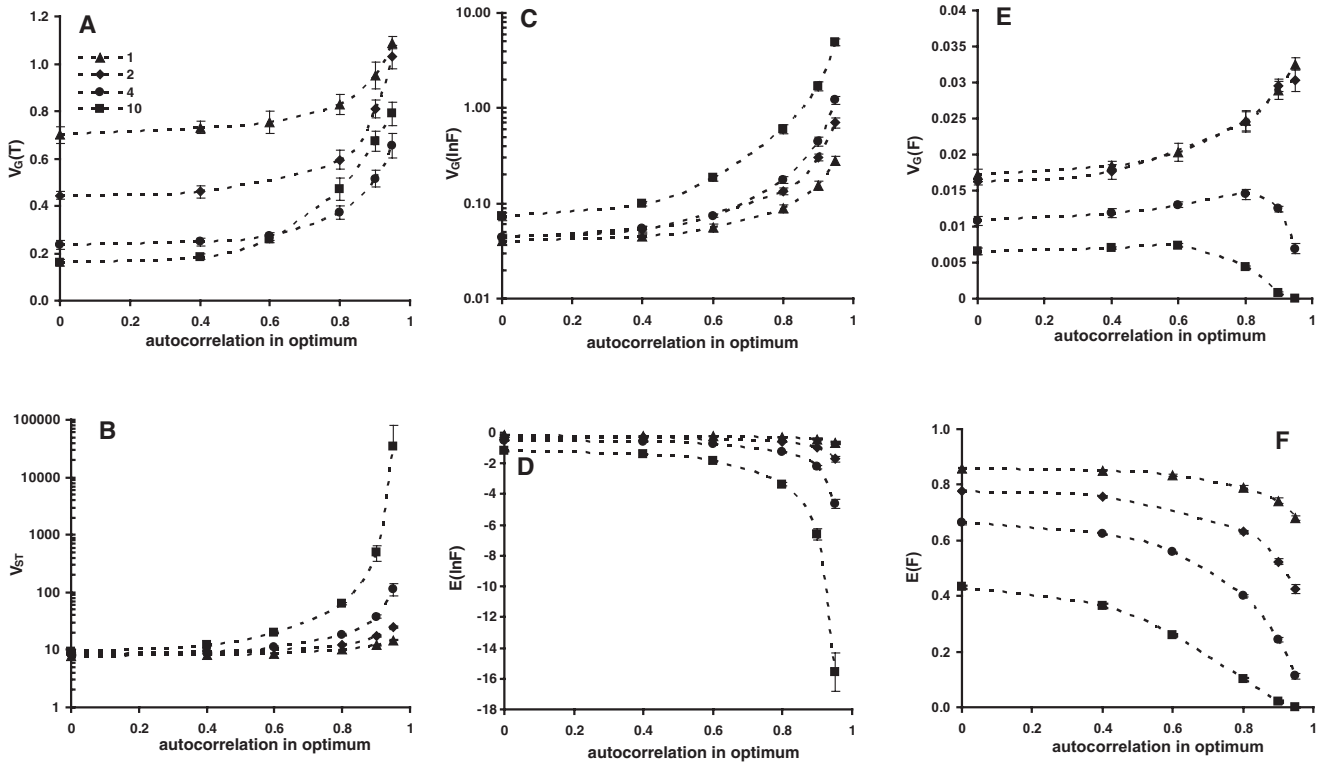

Figure 5. Influence of autocorrelation in the optimum between generations on (A) genetic variance of a quantitative trait, (B) the inverse of the strength of apparent stabilizing selection on a quantitative trait (V_{ST}), (C) genetic variance in $\log_e$ fitness, (D) average of $\log_e$ fitness, (E) genetic variance in fitness, and (F) average of fitness. Model and simulation otherwise are as Figure 2, with the optimum following equation (4) among generations. The results were shown for the situation of n = 1, 2, 4, and 10 and for variance of white noise δ_i: V_i = 1.0.

the optimum randomly changes with magnitude $\sqrt{V}_o = 1.0\sigma_E$. As in the case of a directionally moving optimum, this relative increase becomes substantially higher when λ becomes small, five-fold (from $V_G(F) = 4.5 \times 10^{-4}$ to 2.1×10^{-3}), for example, when $\lambda = 0.005$. The relative increase in V_G(T) is comparatively weak. For data shown in Fig. 4, there is a 1.2- to 2.3-fold increase in V_G(T) and a 3.4- to 4.8-fold increase in V_G(F) for n increasing from 1 to 10 when the optimum randomly changes with $\sqrt{V}_o = 1.0\sigma_E$. However, there is a substantial increase in V_G(lnF): under the same conditions the increase is from six- to 32-fold as n increases from 1 to 10.

Equations (21) and (22) were obtained assuming a randomly and slowly changing optimum so that the population stays near MSB. If the optimum changes drastically, the expressions become invalid, and the capacity for adaptation from both new mutations and segregating variance might be insufficient to enable the population to avoid extinction (Gomulkiewicz and Holt 1995).

MARKOV PROCESS

The impact of autocorrelation in the optimum between generations under white noise with variance $V = 1.0V_E$ is weak unless the autocorrelation coefficient d exceeds 0.8 (Fig. 5; Table S3). Autocorrelation significantly increases V_G(T) and V_G(lnF), but reduces E(F) (Fig. 5). For example, when $d = 0.9$, the increase in V_G(T) is <2.2-fold for $n < 10$ and 4.2-fold for $n = 10$ traits, and in V_G(lnF) is 3.8-, 6.8-, 10-, and 24-fold for $n = 1$, 2, 4, and 10 traits, respectively (Fig. 5). The pattern of change in V_G(F) with autocorrelation is different. When only one or two traits are under stabilizing selection so the total selection is not strong, autocorrelation increases V_G(F), for example, about two-fold when the autocorrelation = 0.9. With more traits so that mutant alleles are under strong selection, V_G(F) first increases and then decreases with autocorrelation (Fig. 5; Table S3). The different behaviors of V_G(F) and V_G(lnF) with autocorrelation have the following explanation. When autocorrelation increases and approaches 1.0, so the variance of changing optimum becomes very large, the fitness becomes very small (Fig. 5D and F) and can vary within only a small range; while $\log_e$ fitness can vary much more and V_G(lnF) can remain high. As for the above two types of changing optimum, the relative increase becomes substantially higher as the mutation rate becomes small (Table S3). The autocorrelation weakens the apparent stabilizing selection (i.e., increasing the value of V_{ST}) (Fig. 5B; Table S3).

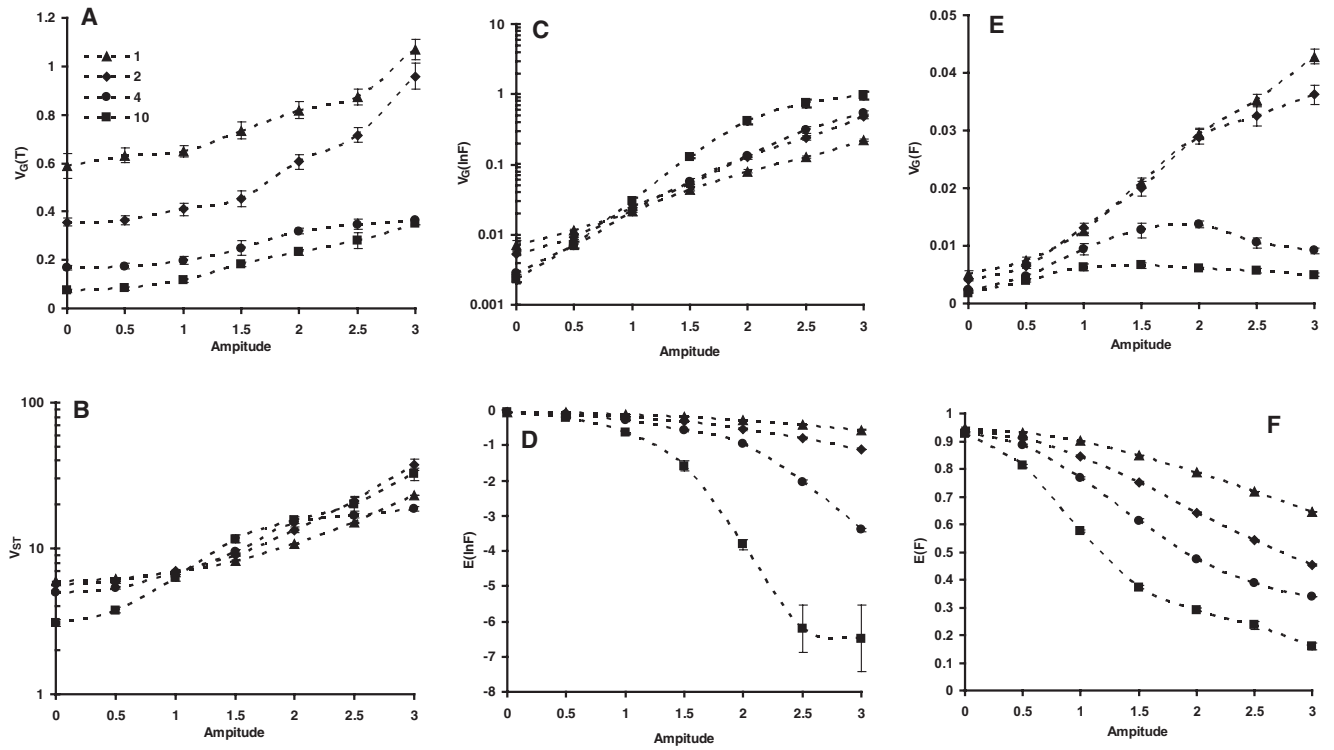

Figure 6. Influence of a periodically changing optimum on (A) genetic variance of a quantitative trait, (B) the inverse of the strength of apparent stabilizing selection on a quantitative trait (V_{ST}), (C) genetic variance in $\log_e$ fitness, (D) average of $\log_e$ fitness, (E) genetic variance in fitness, and (F) average of fitness. Model and simulation otherwise are as Figure 2. The real stabilizing selection with a Gaussian fitness function acts independently on each of n identical traits with independent optima changing as in equation (5) with period $P = 20$ generations. The situations of $n = 1$, 2, 4, and 10 are illustrated.

It is illuminating to compare the optimum that follows a linear stationary Markov process with directionally and randomly moving optima. Superficially, the moving optimum described by (4) is just a sum of Gaussian white noise and the effects of a directionally moving optimum: it reduces to the latter when the variance of white noise $(V) = 0$ and to a randomly moving optimum when the autocorrelation $(d) = 0$. Its variance among generations $V_O = V/(1 - d)^2$ is determined by both V and d. For small V, the increase in genetic variance with autocorrelation is larger than for large V (data not shown). If V is very small the increase of genetic variance with autocorrelation will thus become similar to that for a directionally moving optimum; whereas if d is very small, it will be similar to that for a randomly moving optimum. Therefore, the optimum that follows a linear stationary Markov process is somewhere between a directionally and a randomly moving optimum (further supported by detailed analysis, see Table 1).

PERIODICALLY CHANGING OPTIMUM

$V_G(T)$ increases with the amplitude of the change (Fig. 6; Table S4), as for stabilizing selection on a single trait (Bürger 1999). The increase relative to that for a constant optimum is, however, higher with more traits: for example, for a scenario of period $P = 20$ generations and amplitude $A = 3\sigma_E$, $V_G(T)$ increases 1.8-, 2.2-, and 4.8-fold for $n = 1$, 4, and 10 traits, respectively (Fig. 6A). The overall strength of apparent stabilizing selection on each trait reduces (i.e., V_{ST} increases), increasingly so with more traits (Fig. 5B). The mean fitness decreases and $V_G(\ln F)$ increases with increasing amplitude. Similarly, the reduction in $E(F)$ is greater with more traits: for example, under the same scenario, by 32%, 64%, and 83% for $n = 1$, 4, and 10 traits, respectively (Fig. 6F) and, the relative increase in $V_G(\ln F)$ is higher: 31-, 192-, and 411-fold increase, respectively (Fig. 6C). The patterns of $V_G(F)$ with amplitude are different (Fig. 6E). When there are only one or two traits under stabilizing selection, $V_G(F)$ increases with amplitude, and the relative increase is about eight-fold when $A = 3\sigma_E$. When there are more traits, mutant alleles are under strong selection and $V_G(F)$ first increases with increasing amplitude to a maximum, then decreases. $V_G(\ln F)$ and $V_G(F)$ behave differently because fitness values are extremely low if the optimum is autocorrelated among generations. As in the above three types of environmental change, the relative increase becomes higher when the mutation rate becomes small (Table S4). Numerical simulations show that variances change more with the amplitude than with the period (data not shown), so we do not show the results for changing patterns with different periods.

Discussion

Although variance in fitness is the fuel of adaptation (Fisher 1958) and fitness is fundamental to our understanding of adaptation, our knowledge is very limited of what determines fitness and how it relates to other quantitative traits. To understand how the genetic variance in fitness can be sufficient for adaptation, in this study fitness is quantified via multivariate stabilizing selection in accordance with Fisher's geometrical model. To simplify the analysis, we assume random mating, free recombination, additivity within and between loci, and strengths of both stabilizing selection and mutational effects on traits are uncorrelated, as are those between them. Our investigations show that, in a constant environment, a high level of genetic variance in fitness can be maintained under MSB only in populations that have a high mutation rate. If, however, there is a changing optimum, stabilizing selection can lead to a considerable increase in the level of genetic variance in fitness, although mean fitness is reduced. This increase in variance relative to that in a constant environment is large when the mutation rate is low, and therefore MSB in a changing environment can maintain sufficient genetic variance in fitness for adaptation. Whereas intuitive and naïve theory based on the simple action of natural selection predicts that variance in fitness would be lost, in contrast to empirical observations, our more detailed investigations show this paradox vanishes and that variance is available in the face of strong selection.

ADAPTATION VERSUS COMPLEXITY

In a constant environment, it is well known that the mean fitness is simply determined by the mutation rate (the mutation load is twice the mutation rate under WMSS, Haldane 1932). The mean fitness is therefore independent of the number (n) of independent traits under selection (i.e., "organismal complexity," or degree of pleiotropy [Orr 2000]), however, its genetic variance $V_G(F)$ is closely associated with n. We found that $V_G(F)$ is determined by two components. The first is the input of new mutations, which is proportional to the mutational variance in quantitative traits (V_M), while the second can be understood as the contribution from their standing genetic variance and is proportional to the square of the genomic mutation rate (see (13), (16) and Fig. 1C). These two components are related. For example, organisms which have a high mutation rate may have a high V_M and therefore can maintain high $V_G(F)$ and have high capacity of adaptation to a changing environment.

The $V_G(F)$ is influenced by organismal complexity through a U-shaped relationship because with increasing organismal complexity the first component increases but the second decreases. The relationship stems from the so-called Euclidean superposition mutation model and MSB. In the Euclidean superposition model, which has been supported by empirical data (Wagner et al. 2008; Wagner and Zhang 2011; Hill and Zhang 2012), mutational effects on individual traits are independent of the total number of traits affected and the total impact of mutations increases linearly with the degree of pleiotropy. Thus, the total mutational variance increases with n. (If the invariant total effect model [Orr 2000] was assumed, this term would be constant across n values, however.) At MSB, those mutations that affect more traits are under stronger selection, which leads to the decrease in quantitative genetic variance (see (15)) and its consequent contribution to $V_G(F)$ (second term of (16)). Therefore, the initial decrease in $V_G(F)$ with n is due to the increased selection pressure whereas the increase for large n is due to the increased overall mutational effect, implying that very complex organisms can have high genetic variance.

Another relevant question is: how much of $V_G(F)$ maintained within the current environment is usable for future new environments? Unlike a quantitative trait (e.g., body weight) that is only determined by gene effects if phenotypic plasticity is ignored, the fitness effects of genes are also determined by the effects of the environment on the selection applied. If we assume that fitness effects of genes do not change dramatically when the population changes from its current to a future new environment, the genetic variance in fitness maintained in the current equilibrium population can provide usable fuel for adaptation to future new environments. Therefore the U-shaped relationship of $V_G(F)$ with n indicates that a very complex organism can also have a high rate of adaptation in accordance with Fisher's fundamental theorem (1958).

This finding is in sharp contrast to that predicted in the so-called "cost of complexity" theory (Orr 2000) in which the rate of adaptation decreases quickly with increasing organismal complexity (i.e., n). This discrepancy arises because Orr (2000) considers only the contribution of "beneficial" new mutant alleles and, because the possibility that mutation can help populations to catch up with the new optimum decreases with the degree of pleiotropy (n), the rate of adaptation decreases with n. In principle, adaptation relies not only on new mutations but also on the standing genetic variance (Crow 2008; Wagner and Zhang 2011). Our results combine both; as the contribution from *all* mutations (i.e., the first component of (16)) increases with organismal complexity, the rate of adaptation does not correspondingly decrease monotonically. For organisms that have a high mutation rate, say one mutation per genome per generation, standing quantitative genetic variation is the main source of $V_G(F)$ when organismal complexity is low; with increasing organismal complexity, its contribution decreases but that from mutation increases such that for very complex organisms, the main contribution to adaptation is from mutations. This argument still holds for populations in a randomly changing environment (see (22)).

DISTRIBUTION AND PLEIOTROPY OF MUTATIONAL EFFECTS

For the fitness landscape determined by multivariate stabilizing selection, the distribution of fitness effects of mutations is determined by the number of independent traits under stabilizing selection (equivalently the degree of pleiotropy). With a low degree of pleiotropy, the distribution is leptokurtic (i.e., L-shaped), and approaches the normal with increasing degree of pleiotropy (Zhang and Hill 2003). The L-shaped distributions of mutational effects on fitness, inferred from empirical mutational accumulation and sequence data (Eyre-Walker and Keightley 2007), suggest that the degree of pleiotropy must be small if Fisher's geometrical model of fitness applies. Although pleiotropy is a common phenomenon (Lynch and Walsh 1998; Barton and Keightley 2002; Mackay 2004; Ostrowski et al. 2005; Weedon and Frayling 2008; Wagner et al. 2008; Wang et al. 2010), the degree of pleiotropy cannot be large (Zhang and Hill 2003; McGuigan et al. 2011). This reasoning was further supported by a detailed analysis by Martin and Lenormand (2006a), which suggests that the number of independent traits could be very small ($n < 3$) for some model species. For such organisms with low complexity, their genetic variance in fitness can be high only if their mutation rate is high, say $\lambda \geq 0.3$ mutations per haploid genome per generation.

CHANGING ENVIRONMENT AS A MAGNIFIER

No living organism lives in a constant environment, so it is important to understand how populations respond to and are sustained in a changing environment. To explore the impact of changing environment on the genetic variances, we only consider independent and symmetric scenarios where independence of both stabilizing selection and mutational effects on multiple identical traits and of the changes in optimal values among traits is assumed.

Whether the optimum changes directionally, randomly, or periodically, the mean fitness is reduced but its variance increased. Therefore, a changing environment drives the population to experience extinction risk by decreasing its overall fitness but complements it with increasing potential to avoid it via an increased genetic variance (Gomulkiewicz and Holt 1995). This is the consequence of a complicated process. For a population in a varying environment, the mean fitness is actually the long-term average of mean fitness (see (11)). Although the overall mean fitness remains unchanged, its mean fitness changes between generations. With a continuous moving optimum that reduces mean fitness, it is the increase in mean fitness by natural selection that offsets the deterioration caused by varying environmental conditions. Under a constant environment, most mutations are deleterious. However, if the environment is changing, some deleterious mutants could become beneficial and increase in frequency in a new environment and contribute more genetic variance. It is the genetic variance maintained in previous generations that natural selection uses to increase mean fitness. Results (Figs. 2F, 4F, 6F, eqs. 20 and 24) show that the increase in mean fitness can only partly recover the mean fitness and therefore the overall mean fitness is reduced when the population jumps to new environments.

Although our results show that the increased V_G(F) does not outweigh the effect on lowering E(F) due to deterioration of the environment (Table 1), the increased V_G(F) does provide fuel for the population to adapt to the changing environment. Among the four types of environmental change, which increases V_G(F) most? To answer this a unified criterion is required for measuring the size of change in the optimum, but comparisons are not straightforward because the changes have a distinct nature. Because all types of changing optimum reduce fitness, the estimate of increase in variance per unit of mean fitness loss was used to characterize them. For the same fitness loss, the directionally moving optimum increases variance most (Table 1). Hence, under a directionally moving optimum, the population can maintain a high rate of adaptation and most easily retain its fitness and survive (cf. Charlesworth 1993; Bürger 1999).

For most reasonable estimates of mutation and selection parameters, the increase in V_G(F) can be considerable. For example, with a moderate magnitude of changing optimum, there could be a two- to seven-fold increase relative to that in a constant environment when the mutation rate $\lambda \geq 0.03$ (Figs. 2E, 4E, and 6E) and up to 10- to 30-fold if it is assumed to be very low, say $\lambda = 0.005$ (Tables S1–S4). This behavior is similar to the results given by Waxman and Peck (1999) and Bürger and Gimelfarb (2002), who showed for a single trait that as the mutation rate increases, the rate of increase in V_G(T) due to a directionally changing optimum reduces. Hence, a changing environment works as a magnifier: its impact becomes strong for populations with low mutation rate so that their V_G(F) is retained at intermediate levels. Thus, both mutation and changing environment facilitate maintenance of genetic variance (cf. Crow 2008).

GAUSSIAN VERSUS QUADRATIC FITNESS FUNCTIONS

Turelli (1988) and Bürger (1999) showed for a single trait that a randomly changing optimum cannot increase quantitative genetic variance, which differs from our results (Fig. 4A, B; Table S2). The discrepancy arises because different fitness functions, quadratic in Turelli (1988) and Gaussian here, and different parameter ranges were used (Bürger 1999). In a constant environment, these fitness functions are roughly the same under weak selection. Otherwise the quadratic fitness function represents increasingly stronger selection than the Gaussian. Then a lower V_G(T) but a higher V_G(F) maintained under quadratic stabilizing selection than those under Gaussian stabilizing selection, all others being the same (Fig. 1).

When the optimum changes randomly, this difference between two types of selection causes qualitative change in the behavior of the genetic variance: $V_G(F)$ increases under both types of selection while $V_G(T)$ increases under Gaussian stabilizing selection (Fig. 4; Table S2) but not under quadratic stabilizing selection (Turelli 1988). To illustrate this, we consider a simple example. Consider one trait under stabilizing selection with $V_S = 2.5V_E$ and mutation rate $\lambda = 0.01$ per haploid genome per generation. To reveal the difference caused by model parameters, two sets of population size and number of loci in the whole genome (N, L) are considered: (250,100) and (500,200) regarded as a "small population" and a "large population," respectively, the smaller population representing relatively weak overall selection but high per locus mutation rate and the larger relatively strong overall selection but low per locus mutation rate. Under Gaussian stabilizing selection, numerical simulations show that $V_G(T) = 0.084 \pm 0.002$ when the variance in the optimum is $V_O = 0$ and $V_G(T) = 0.102 \pm 0.047$ when $V_O = 1.0$ for the "smaller population," and both $V_G(T)$ are close to the theoretical prediction 0.1. However, $V_G(T) = 0.101 \pm 0.010$ for $V_O = 0$, and 0.142 ± 0.070 for $V_O = 1.0$ for the "larger population," showing a clear increase in $V_G(T)$ with V_O. This difference is caused by the stronger linkage disequilibrium in the "smaller population" (cf. Zhang and Hill 2003). Under quadratic stabilizing selection, even within the "larger population," $V_G(T) = 0.099 \pm 0.004, 0.074 \pm 0.003$ when $V_O = 0.0, 1.0$, respectively. This illustration may also provide an explanation of why an increase in $V_G(T)$ was not detected by Bürger (1999) who assumed a small number of loci and hence a high per locus mutation rate.

This qualitative difference between two types of selection can be explained as follows. Under quadratic stabilizing selection, mutants of large effects become lost more easily with increasing fluctuations in the optimum and individuals that deviate far from the optimum (i.e., $> \sqrt{2V_S}$) are removed. Although mutants of small effects on quantitative traits increase because of weakened selection (see (9)), $V_G(T)$ can hardly increase. With increasing V_O, the squared selective values increase (see (B4)), which leads to increased $V_G(F)$. Under Gaussian stabilizing selection, mutants of large effect can survive at a very low frequency and contribute to $V_G(T)$ and $V_G(F)$, increasingly so with increasing fluctuations in the optimum (Fig. 4 and Table S2). When the optimum changes directionally, mutant alleles that help the population mean to catch up with the moving optimum become beneficial and increase in frequency, therefore genetic variance increases under both forms of stabilizing selection (Bürger 1999; Waxman and Peck 1999; Fig. 2 and Table S1).

SIMPLIFICATION VERSUS GENERALITY

Our analyses are based on what Martin and Gandon (2010) refer to as the isotropic model (i.e., various traits are independently identical), but they show that the anisotropic model reduces approximately to the isotropic model when the dimension becomes smaller. Zhang and Hill (2003) showed that multiple symmetric traits can provide a good approximation for the asymmetric selection if the variation in strength is not large. Moreover, the Gaussian distribution has been assumed for the mutational effects on quantitative traits, being consistent with the analysis of mutational effects (Martin and Lenormand 2006b; Wang et al. 2010). If we assume that mutational effects follow a more kurtotic distribution, such as the exponential or Wishart (Zhang et al. 2002), $V_G(T)$ in each trait cannot change greatly if the multivariate stabilizing selection is nearly symmetric (Zhang and Hill 2003). This conclusion is expected also to apply to the genetic variance in fitness because $V_G(F)$ and $V_G(T)$ have similar behavior (Figs. 2A and E, 4A and E).

Complicated models that include correlation in mutational effects and selection on multiple traits can be reduced to the simple model considered here by a transformation that simultaneously diagonalizes both matrices **M** and **S** (Zhang and Hill 2003). The effective number of independent traits (n) would then be much smaller than the actual number of traits (Zhang and Hill 2003; Hine and Blows 2006; McGuigan 2011). Theoretical models that include correlated mutational effects and stabilizing selection have been proposed (Arnold et al. 2008; McGuigan et al. 2011), but show that correlations do not greatly alter the average single-generation changes in the genetic variance–covariance matrix (Jones et al. 2004, 2007). Zhang and Hill (2003) showed that correlations in mutational effects and selection on multiple traits can change the predictions of $V_G(T)$ significantly only if they are very strong (>75%). As argued above, this conclusion also applies to $V_G(F)$ and therefore our results for the independent and symmetric situations could be a reasonable approximation for the more general and complicated situations. We also assume that the optimal values are independent among multiple traits. Numerical simulations (not shown) for two trait situations also indicate that the impact of correlation in optimal values is weak unless the correlation is extremely strong.

We have also neglected many other complicating factors such as genotype-environment interaction, nonadditivity of gene action (dominance and epistasis), and linkage. Gene interactions within and between loci may be common (Crow 2008), but data and theory show that quantitative genetic variance is mostly additive, not least for models such as are analyzed here where mutant gene frequencies tend to be extreme (Hill et al. 2008). Zhang and Hill (2003) concluded that although linkage disequilibrium can reduce quantitative genetic variance, its effect is weak. Because natural selection acts on phenotype, genotype-environment interaction such as phenotypic plasticity can influence the level of phenotypic variance (Zhang 2005). Investigations that include genotype-environment interactions and environmental constraints

in the model can help us understand the level of the residual variance (Teplitsky et al. 2009; McGuigan et al. 2011) and thus total variance in fitness. Other mechanisms such as migration, heterogeneous environments, and heterozygote superiority certainly contribute to genetic variance in fitness (Barton 1990; Stearns and Hoekstra 2000; Crow 2008). Zhang (2006) showed a complex pattern of effects of migration and heterogeneous environment: both mutation rate and temporal variation in environment increase quantitative genetic variance, but both migration rate and spatial variation in environment decrease it. How these factors interact to contribute to the variance in fitness is worth further investigation.

Conclusion

Although many other factors (Barton 1990; Stearns and Hoekstra 2000; Crow 2008) can contribute to the maintenance of genetic variance in fitness, our investigations show that both mutation and changing environment are important contributors and suggest that MSB within a changing environment is a possible mechanism for its maintenance. Moreover, our analyses, combined with elegant analyses of mutational effects on fitness by Martin and Lenormand (2006a,b), lend further support to Fisher's geometrical model as a possible model for fitness landscape.

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Appendix A: Genetic Variance in Fitness under Constant Optima

If the population mean phenotype at generation t is $\mathbf{z}_t$, the mutant of effect $\mathbf{a}$ will change the phenotype to $\mathbf{z}_t + \mathbf{a}$ and the mutant phenotype will have fitness $W(\mathbf{z}_t + \mathbf{a}) = \exp\{-\frac{1}{2}(\mathbf{z}_t + \mathbf{a} - \mathbf{o}_t)^{\mathrm{T}}\mathbf{S}(\mathbf{z}_t + \mathbf{a} - \mathbf{o}_t)\}$. Its selection coefficient relative to the population mean is defined as

$$s = W(\mathbf{z}_t + \mathbf{a})/W(\mathbf{z}_t) - 1 \tag{A1}$$

or equivalently as

$$Q = \ln(1+s) = \ln[W(\mathbf{z}_t + \mathbf{a})/W(\mathbf{z}_t)] = -\frac{1}{2}[(\mathbf{z}_t - \mathbf{o}_t)^{\mathrm{T}}\mathbf{S}\mathbf{a} + \mathbf{a}^{\mathrm{T}}\mathbf{S}(\mathbf{z}_t - \mathbf{o}_t) + \mathbf{a}^{\mathrm{T}}\mathbf{S}\mathbf{a}]. \tag{A2}$$

The selective value comes from two parts: directional selection due to deviation of wild type from optimum and stabilizing

selection due to mutation. The mean phenotype will be coincident with the optimum when the optimum remains constant, that is, $\mathbf{z}_t = \mathbf{o}_t$ (Bürger 2000). Assume that the n traits are independent and identical and under independent stabilizing selection such that $\mathbf{S} = \zeta^2\mathbf{I}$. Under weak selection whereby Gaussian and quadratic fitness functions are approximately equal the selective value of the mutation is approximately

$$s = -\frac{1}{2}\sum_{j=1}^{n} a_j^2\zeta^2. \tag{A3}$$

Because of complicated interactions in fitness effects between alleles within and across loci (Martin et al. 2007), it is not straightforward to obtain the expression for $V_{\mathrm{G}}(\mathrm{F})$ in terms of fitness effects of mutant alleles as (6) for $V_{\mathrm{G}}(\mathrm{T})$. However, by definition, the variance in fitness can be expressed indirectly via mutational effects on traits as

$$V_{\mathrm{G}}(\mathrm{F}) \equiv E(s^2) - E^2(s) = \zeta^4\sum_{k=1}^{n}\sum_{j=1}^{n} V_{G_{kj}}(\mathrm{T}), \tag{A4}$$

where the variance–covariance of the product of deviations from mean of traits k and j under the infinite independent loci model (Zhang et al. 2002) is

$$\begin{aligned} V_{G_{kj}}(\mathrm{T}) &= E[(z_k-\overline{z}_k)^2(z_j-\overline{z}_j)^2] - E[(z_k-\overline{z}_k)^2]E[(z_j-\overline{z}_j)^2] \\ &= \int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty} f(\mathbf{a})[H(s)-3K(s)]\frac{a_i^2a_j^2}{16}d\mathbf{a} + 2[G_{kj}(T)]^2 \end{aligned} \tag{A5}$$

and the genetic variance–covariance in quantitative traits is

$$G_{kj}(\mathrm{T}) = \int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty} f(\mathbf{a})H(s)\frac{a_k a_j}{4}d\mathbf{a}, \tag{A6}$$

(Zhang and Hill 2003). Here, $f(\mathbf{a})$ is the joint distribution of mutational effects on n traits. Hence, $V_{\mathrm{G}}(\mathrm{F})$ is determined by the product of ζ^4 and the sum of fourth moments $V_{G_{kj}}(\mathrm{T})$ of mutational effects on quantitative traits. If we regard ζ^2 as representing the one-fold action of stabilizing selection, ζ^4 represents the two-fold action of stabilizing selection. This suggests that variance in fitness is a consequence of fourth moments of mutational effects under the two-fold action of stabilizing selection.

Expressions for heterozygosity $H(s)$ and square of heterozygosity $K(s)$ were given by Kimura (1969). By the independence assumption of mutational effects, the distribution $f(\boldsymbol{a})$ reduces to $\Pi\, g_j(a_j)$,

$$G_{kj}(\mathrm{T}) = \delta_{kj}V_{\mathrm{G},j}(\mathrm{T}) = \delta_{kj}\int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty}\prod_{j=1}^{n} g_j(a_j)H(s)\frac{a_j^2}{4}d\mathbf{a}. \tag{A7}$$

Here, δ_{kj} is a Kronecker delta: $\delta_{kj} = 1$ if $k = j$, $\delta_{kj} = 0$ otherwise. In a large population such that $2N|s| >> 1$, the heterozygosity at mutation-selection-drift balance can be approximated by

$$H = 4\lambda/(-s) \tag{A8}$$

and

$$K \cong 0 \tag{A9}$$

(Kimura 1969), where λ is the haploid genomic mutation rate. The above expressions can be simplified as follows: genetic variance maintained on trait j,

$$V_{\mathrm{G},j}(\mathrm{T}) = \int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty} g_1(a_1)\ldots g_n(a_n)\frac{\lambda a_j^2}{\zeta^2\sum_{l=1}^{n}\frac{1}{2}a_l^2}d\mathbf{a}, \quad j = 1,\ldots,n, \tag{A10}$$

variance–covariance of the product of deviations from mean of traits k and j,

$$V_{G_{kj}}(\mathrm{T}) = \int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty} g_1(a_1)\ldots g_n(a_n)\frac{4\lambda}{\sum_{l=1}^{n}\frac{1}{2}a_l^2\zeta_l^2}\frac{a_k^2a_j^2}{16}d\mathbf{a} + 2\delta_{kj}V_{\mathrm{G},j}(\mathrm{T})^2. \tag{A11}$$

Notice that

$$\sum_{k=1}^{n}\sum_{j=1}^{n} a_k^2a_j^2 = \left(\sum_{k=1}^{n} a_k^2\right)\left(\sum_{j=1}^{n} a_j^2\right) \tag{A12}$$

and after some algebra the genetic variance in fitness simplifies to

$$V_{\mathrm{G}}(\mathrm{F}) = \frac{1}{2}\lambda\sum_{j=1}^{n}\zeta_j^2\int_{-\infty}^{\infty} a_j^2g_j(a_j)da_j + 2\sum_{j=1}^{n}\left(V_{\mathrm{G},j}(\mathrm{T})\zeta_{\mathrm{j}}^2\right)^2. \tag{A13}$$

Note that the mutational variance in trait j per generation is $V_{\mathrm{M},j} = \frac{1}{2}\lambda\int_{-\infty}^{\infty} a_j^2g_j(a_j)da_j$,

$$V_{\mathrm{G}}(\mathrm{F}) = \sum_{j=1}^{n}\zeta_j^2[V_{\mathrm{M},j} + 2(V_{\mathrm{G},j}(\mathrm{T})\zeta_{\mathrm{j}})^2]. \tag{A14}$$

The expression for $V_{\mathrm{G},j}(\mathrm{T})$ is given by Zhang and Hill (2003) for some special situations. Under the independent and symmetric situation of the same strength of stabilizing selection $\zeta_j^2 = 1/(2V_{\mathrm{S}})$ and the same mutational variance $V_{\mathrm{M},j} = V_{\mathrm{M}}, j = 1,\ldots,n$, on all traits

$$V_{\mathrm{G},j}(\mathrm{T}) = V_{\mathrm{G}}(\mathrm{T}) = 4\lambda V_{\mathrm{S}}/n. \tag{A15}$$

$$V_{\mathrm{G}}(\mathrm{F}) = \frac{nV_{\mathrm{M}}}{2V_{\mathrm{S}}} + \frac{8\lambda^2}{n}. \tag{A16}$$

Monte-Carlo simulations show that the prediction (A16) is a good approximation to the numerical results when mutation is weak and selection is strong (i.e., more traits under selection) (Fig. 1C).

Appendix B: Genetic Variance in Fitness under Randomly Varying Optima

To simplify derivations, we consider only the situation where the n traits have identically independent stabilizing selection and mutational effects. We assume that the optimum $\mathbf{o}_t$ changes randomly across generations. The selective value of the mutation at generation t can be approximated as

$$s_t \approx Q_t = -\zeta^2 \sum_{j=1}^{n} \left[\frac{1}{2} a_j^2 - (o_{j,t} - z_{j,t})^2 a_j^2 \zeta^2 - (o_{j,t} - z_{j,t}) a_j \right] \tag{B1}$$

and its square as

$$\begin{aligned} s_t^2 = {} & \zeta^4 \sum_{j=1}^{n} \left[\frac{1}{2} a_j^2 - (o_{j,t} - z_{j,t})^2 a_j^2 \zeta^2 - (o_{j,t} - z_{j,t}) a_j \right]^2 \\ & + \zeta^4 \sum_{k \neq j}^{n} \left[\frac{1}{2} a_k^2 - (o_{k,t} - z_{k,t})^2 a_k^2 \zeta^2 - (o_{k,t} - z_{k,t}) a_k \right] \\ & \times \left[\frac{1}{2} a_j^2 - (o_{j,t} - z_{j,t})^2 a_j^2 \zeta^2 - (o_{j,t} - z_{j,t}) a_j \right], \end{aligned} \tag{B2}$$

where $z_{j,t}$ is the average of mean phenotype of trait j at generation t.

If the optimum is sampled from $N(\mathbf{0}, \mathbf{I}\sigma_o^2)$, the average value of the trait mean is zero and its variance is very small relative to ${\sigma_o}^2$ (see Fig. 3). Assuming that $o_{j,t} - z_{j,t}, j = 1, \ldots, n$, are independently normal, and averaging over a long period, the following approximations hold,

$$E_T[(o_{k,t} - z_{k,t})^{2m+1} (o_{j,t} - z_{j,t})^{2n+1}] \approx 0, \quad m = n = 0, 1, 2 \ldots$$

$$E_T[(o_{j,t} - z_{j,t})^2] \approx \mathrm{Var}(o_j) = V_O$$

$$E_T[(o_{j,t} - z_{j,t})^4] \approx 3V_O^2$$

$$E_T[(o_{k,t} - z_{k,t})^2 (o_{j,t} - z_{j,t})^2] \approx \mathrm{Var}(o_k)\mathrm{Var}(o_j) = V_O^2.$$

Employing these following approximations

$$\begin{aligned} & E_T \left\{ \sum_{k,j}^{n} \left[\frac{1}{2} a_k^2 - (o_{k,t} - z_{k,t})^2 a_k^2 \zeta^2 - (o_{k,t} - z_{k,t}) a_i \right] \right. \\ & \quad \left. \times \left[\frac{1}{2} a_j^2 - (o_{j,t} - z_{j,t})^2 a_j^2 \zeta^2 - (o_{j,t} - z_{j,t}) a_j \right] \right\} \\ & = \sum_{k,j}^{n} \left\{ \frac{1}{4} a_k^2 a_j^2 [1 - 2V_O \zeta^2]^2 + \delta_{kj} \left[2V_O^2 a_j^4 \zeta^4 + V_O a_j^2 \right] \right\} \end{aligned}$$

the means of selective value and its square of the mutant allele over generations are approximated as

$$\hat{s} \equiv E_T[s_t] \approx E_T[Q_t] = -\zeta^2 \sum_{j=1}^{n} \left[\frac{1}{2} a_j^2 (1 - 2V_O \zeta^2) \right] \tag{B3}$$

$$\begin{aligned} \hat{s^2} \equiv E_T\left[s_t^2\right] \approx E_T\left[Q_t^2\right] = \zeta^4 & \left\{ \left(\sum_{j=1}^{n} \frac{1}{2} a_j^2 [1 - 2V_O \zeta^2] \right)^2 \right. \\ & \left. + \sum_{j=1}^{n} \left[2V_O^2 a_j^4 \zeta^4 + V_O a_j^2 \right] \right\}, \end{aligned} \tag{B4}$$

respectively.

We assume that the optimum changes slowly and over a small scale so that the fluctuation in s remains small and the population remains near the MSB. The average heterozygosity over generations can then be approximated by the delta method (Lynch and Walsh 1998) as $H = \frac{4\lambda}{\hat{s}} \frac{\hat{s^2}}{\hat{s}^2}$. Furthermore, use of the Fisher–Wright transition matrix confirms that, when the magnitude of fluctuation in optimum is much smaller than the width of fitness profile (i.e., $V_O << V_S$), $\hat{s^2} \approx \hat{s}^2$ and $H \approx 4\lambda/\hat{s}$. As in Appendix A, the average genetic variance in a quantitative trait and fitness over a long period can be approximated by

$$V_{G,j}(\mathrm{T}) = \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \frac{\lambda a_j^2}{\sum_{k=1}^{n} \frac{1}{2} a_k^2 \zeta^2 (1 - 2V_O \zeta^2)} \prod_{k=1}^{n} g_k(a_k) da_k. \tag{B5}$$

$$\begin{aligned} V_G(\mathrm{F}) = {} & \sum_{k=1}^{n} \sum_{j=1}^{n} \zeta_k^2 \zeta_j^2 V_{G_{kj}} \approx \frac{1}{2} \lambda \zeta^2 (1 - 2V_O \zeta^2) \\ & \times \sum_{j=1}^{n} \int_{-\infty}^{\infty} a_j^2 g_j(a_j) da_j + \lambda \zeta^4 \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \\ & \times \frac{\sum_{j=1}^{n} V_O \left[a_j^2 + a_j^4 V_O \zeta^4 \right]}{\sum_{k=1}^{n} \frac{1}{2} a_k^2 \zeta^2 (1 - 2V_O \zeta^2)} \prod_{k=1}^{n} g_k(a_k) da_k + 2 \sum_{j=1}^{n} V_{G,j}^2 \zeta^4 \\ = {} & \zeta^2 (1 - 2V_O \zeta^2) \sum_{j=1}^{n} V_{M,j} + \frac{2\lambda \zeta^2 V_O}{(1 - 2V_O \zeta^2)} + \frac{2\lambda V_O^2 \zeta^6}{(1 - 2V_O \zeta^2)} \\ & \times \int_{-\infty}^{\infty} \cdots \int_{-\infty}^{\infty} \frac{\sum_{j=1}^{n} a_j^4}{\sum_{k=1}^{n} a_k^2} \prod_{k=1}^{n} g_k(a_k) da_k + 2\zeta^4 \sum_{j=1}^{n} V_{G,j}^2. \end{aligned} \tag{B6}$$

Because the n traits are identically independent, and further noting that

$$\frac{1}{2}\lambda\int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty}\frac{\sum_{j=1}^{n}a_j^4}{\sum_{k=1}^{n}a_k^2}\prod_{k=1}^{n}g_k(a_k)da_k$$

$$< \frac{1}{2}\lambda\int_{-\infty}^{\infty}\cdots\int_{-\infty}^{\infty}\left(\sum_{j=1}^{n}a_j^2\right)\prod_{k=1}^{n}g_k(a_k)da_k = nV_{\mathrm{M}},$$

by approximating the variance to the order of $\mathrm{O}(V_{\mathrm{O}}/V_{\mathrm{S}})$, the above equations reduce to

$$V_{\mathrm{G},j}(\mathrm{T}) = \frac{4\lambda V_S}{n(1-V_{\mathrm{O}}/V_{\mathrm{S}})}. \tag{B7}$$

$$V_{\mathrm{G}}(\mathrm{F}) = \frac{nV_{\mathrm{M}}}{2V_{\mathrm{S}}}(1-V_{\mathrm{O}}/V_{\mathrm{S}}) + \frac{\lambda V_{\mathrm{O}}}{V_{\mathrm{S}}(1-V_{\mathrm{O}}/V_{\mathrm{S}})} + \frac{8\lambda^2}{n(1-V_{\mathrm{O}}/V_{\mathrm{S}})^2}. \tag{B8}$$

These equations were confirmed by numerical simulations (Fig. 4) and show that $V_{\mathrm{G}}(\mathrm{T})$ increases with the magnitude (V_{O}) of fluctuation in the optimum while $V_{\mathrm{G}}(\mathrm{F})$ increases with V_{O} when mutation rate is high, otherwise it may decrease.

Supporting Information

The following supporting information is available for this article:

Table S1. Impact of a directionally moving optimum on $V\mathrm{G}(\mathrm{T})$, $V\mathrm{G}(\mathrm{F})$, $E(\mathrm{F})$, and V_{ST}.
Table S2. Impact of a randomly varying optimum on $V\mathrm{G}(\mathrm{T})$, $V\mathrm{G}(\mathrm{F})$, $E(\mathrm{F})$, and V_{ST}.
Table S3. Impact of autocorrelation in optimum between generations on $V_{\mathrm{G}}(\mathrm{T})$, $V_{\mathrm{G}}(\mathrm{F})$, $E(\mathrm{F})$, and V_{ST}.
Table S4. Impact of a periodically changing optimum on $V\mathrm{G}(\mathrm{T})$, $V\mathrm{G}(\mathrm{F})$, $E(\mathrm{F})$, and V_{ST}.

Supporting Information may be found in the online version of this article.

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SUPPLEMENTARY MATERIAL

Table S1 Impact of a directionally moving optimum on $V_G(T)$, $V_G(F)$, $E(F)$ and V_{ST}. Simulations are obtained for population size $N = 1000$ where there are $L = 3000$ loci on each genome and there are four identical independent traits under real stabilizing selection of Gaussian fitness function with $V_S = 5V_E$ and the optimum moving with a rate κ. For each parameter set, six replicates were generated to obtain their means; and only the means are shown here because standard deviations are of the order of <10% of the means. Note that the mean fitness under fixed optimum is very close to Haldane's formula (i.e. equation (14)). Results are shown for four different mutation rates (λ).

Table S1

	κ=0	κ=0.005	κ=0.01	κ=0.02
λ	$V_G(T)$			
0.005	0.0243	0.123	0.191	0.260
0.01	0.0534	0.147	0.199	0.281
0.03	0.170	0.234	0.302	0.368
0.1	0.616	0.733	0.831	0.943
	$V_G(F)\times10^3$			
0.005	0.445	2.46	4.97	9.45
0.01	0.595	2.63	4.82	9.37
0.03	2.26	4.37	6.69	10.6
0.1	15.6	19.8	23.3	27.5
	$E(F)$			
0.005	0.989	0.926	0.885	0.825
0.01	0.978	0.926	0.896	0.837
0.03	0.934	0.902	0.876	0.838
0.1	0.792	0.759	0.733	0.702
	V_{ST}			
0.005	1.96	4.00	4.87	5.77
0.01	2.90	4.71	5.08	5.84
0.03	5.01	5.56	5.76	6.18
0.1	7.02	7.47	7.86	8.37

Table S2 Impact of a randomly varying optimum on $V_G(T)$, $V_G(F)$, $E(F)$ and V_{ST}. Model and simulation otherwise are as Table S1. The theoretical predictions for $V_G(T)$, $V_G(F)$, and $E(F)$ are from equation (21), (22) and (24) respectively, which are the diffusion approximation under quadratic stabilizing selection. Results are shown for four different mutation rates (λ).

Table S2

	V_O=0		V_O=0.36		V_O=1.0	
	simulations	Predictions	simulations	Predictions	simulations	Predictions
λ	$V_G(T)$					
0.005	0.0243	*0.025*	.0307	*.0269*	0.0400	*0.0313*
0.01	0.0534	*0.05*	.0654	*.0538*	0.0775	*0.0625*
0.03	0.170	*0.15*	.181	*.162*	0.231	*0.188*
0.1	0.616	*0.5*	.700	*.538*	0.820	*0.625*
	$V_G(F)\times10^3$					
0.005	0.445	*0.450*	1.32	*0.817*	2.05	*1.65*
0.01	0.596	*0.600*	2.54	*1.38*	3.78	*3.13*
0.03	2.26	*2.20*	6.81	*4.79*	10.8	*10.6*
0.1	15.6	*20.4*	25.6	*31.4*	30.7	*56.6*
	$E(F)$					
0.005	0.988	*0.990*	0.864	*0.858*	0.711	*0.669*
0.01	0.978	*0.979*	0.851	*0.850*	0.702	*0.667*
0.03	0.934	*0.938*	0.816	*0.824*	0.662	*0.659*
0.1	0.792	*0.819*	0.680	*0.730*	0.545	*0.625*
	V_{ST}					
0.005	1.97	*2.78*	2.49		3.38	
0.01	2.90	*3.33*	3.91		5.12	
0.03	5.01	*4.54*	6.10		8.46	
0.1	7.02	*4.95*	8.82		12.0	

Table S3 Impact of autocorrelation in optimum between generations on $V_G(T)$, $V_G(F)$, $E(F)$ and V_{ST}. Model and simulation otherwise are as Table S1. Results are shown for four different mutation rates (λ).

Table S3

	d=0	0.2	0.6	0.8	0.9	0.95
λ	$V_G(T)$					
0.005	0.0400	0.0446	0.0641	0.145	0.303	0.477
0.01	0.0775	0.0843	0.117	0.198	0.366	0.552
0.03	0.231	0.233	0.272	0.372	0.514	0.654
0.1	0.820	0.832	0.917	1.08	1.30	1.58
	$V_G(F)\times10^3$					
0.005	2.05	2.28	3.36	6.22	7.30	5.23
0.01	3.78	4.15	6.01	8.31	9.17	6.37
0.03	10.8	10.8	13.0	14.5	12.4	6.91
0.1	30.7	31.1	32.9	31.8	24.8	15.4
	$E(F)$					
0.005	.711	.698	.591	.419	.238	.111
0.01	.702	.687	.589	.414	.241	.121
0.03	.662	.654	.557	.401	.243	.112
0.1	.545	.542	.470	.360	.233	.127
	V_{ST}					
0.005	3.38	3.81	5.79	13.2	34.8	106
0.01	5.12	5.39	7.56	14.8	34.2	100
0.03	8.46	8.53	11.1	17.9	37.6	114
0.1	12.0	12.3	15.2	22.4	42.6	92.3

Table S4 Impact of a periodically changing optimum on V_G(T), V_G(F), E(F) and V_{ST}. Model and simulation otherwise are as Table S1. Results are shown for four different mutation rates (λ).

Table S4

	A=0	1	2	3
λ	V_G(T)			
0.005	0.024	0.032	0.066	0.105
0.01	0.053	0.071	0.130	0.178
0.03	0.170	0.198	0.319	0.365
0.1	0.616	0.717	0.973	1.20
	V_G(F)×10^3			
0.005	0.454	1.69	3.65	3.56
0.01	0.596	3.49	6.57	5.40
0.03	2.26	9.44	13.7	9.17
0.1	15.6	28.8	31.9	22.1
	E(F)			
0.005	0.989	0.817	0.513	0.356
0.01	0.978	0.803	0.501	0.360
0.03	0.934	0.766	0.473	0.339
0.1	0.792	0.645	0.339	0.267
	V_{ST}			
0.005	1.96	2.72	6.92	11.3
0.01	2.90	4.16	10.4	14.2
0.03	5.01	6.80	15.0	18.7
0.1	7.02	9.58	10.6	28.5