

Predicting long-term response to selection

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Summary

Lande's equation for predicting the response of trait means to a shift in optimal trait values is tested using a stochastic simulation model. The simulated population is finite, and each individual has a finite number of loci. Therefore, selection may cause allele frequencies and distributions to change over time. Since the equation assumes constant genetic parameters, the degree to which such allelic changes affect predictions can be examined. Predictions are based only on information available at generation zero of directional selection. The quality of the predictions depends on the nature of allelic distributions in the original population. If allelic effects are approximately normally distributed, as assumed in Lande's Gaussian approximation to the continuum-of-alleles model, the predictions are very accurate, despite small changes in the \mathbf{G} matrix. If allelic effects have a leptokurtic distribution, as is likely in Turelli's 'house-of-cards' approximation, the equation underestimates the rate of response and correlated response, and overestimates the time required for the trait means to reach their equilibrium values. Models with biallelic loci have limits as to the amount of trait divergence possible, since only two allelic values are available at each of a finite set of loci. If the new optimal trait values lie within these limits, predictions are good. If not, singularity in the \mathbf{G} matrix results in suboptimal equilibria, despite the presence of genetic variance for each individual trait.

1. Introduction

Understanding the dynamics of phenotypic evolution is important, not only for predicting how traits should respond to selection, but for knowing how much can be assumed about past selective forces, given present-day trait distributions. Selection experiments have added greatly to our understanding of short-term response, and the results have been, for the most part, consistent with theoretical expectations (Falconer, 1989; Roff, 1997). Patterns of long-term evolutionary change must be studied primarily using non-experimental methods, given the difficulties associated with collecting suitable data.

There is a large body of theoretical work on long-term selection, but most of this concerns mutation-stabilizing selection balance (e.g. Lande, 1975; Turelli, 1984; Barton, 1986; Keightley & Hill, 1988; Burger *et*

al., 1989). These models assume that the population's mean phenotype is already at or near the optimum, and are used primarily for predicting how much genetic variance can be maintained at equilibrium, given various assumptions concerning genetic details. Most directional selection theory is concerned with truncation selection, as used in laboratory experiments (e.g. Robertson, 1970; Bulmer, 1980; Hill, 1982; Keightley & Hill, 1987), and has therefore focussed mainly on short-term responses in small populations. Here, I use a stochastic model to simulate long-term response in finite populations undergoing directional selection to a new set of optimal trait values.

The basic equation for predicting response to a single generation of directional selection is

$$R = h^2 S, \quad (1)$$

where R is the response in the trait mean, h^2 is the narrow-sense heritability, and S is the selection differential. The multivariate version of (1) is

$$\Delta \bar{\mathbf{Z}} = \mathbf{G} \beta \quad (2)$$

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(Lande, 1979), where $\Delta\bar{\mathbf{Z}}$ is a vector of changes in trait means, \mathbf{G} is the genetic variance–covariance matrix, and β is the selection gradient, often written as the product of the inverse of the phenotypic variance–covariance matrix (\mathbf{P}^{-1}) and the vector of selection differentials (\mathbf{s}).

Extending (2) to more than one generation of selection presents two distinct problems. The first is that \mathbf{G} must be assumed to remain constant over time. How likely this is remains controversial, and empirical findings are equivocal (Shaw *et al.*, 1995). The second problem is that directional selection (β) is unlikely to continue at constant intensity for long periods of time in natural populations. Even in experiments using truncation selection, the force of artificial directional selection is likely to be opposed by natural selection, acting either on the selected or on correlated traits (Lande & Arnold, 1983; Zeng & Hill, 1986; Hill & Keightley, 1988). There is strong evidence that stabilizing selection for intermediate trait values is common in nature (Endler, 1986). Therefore, it is of some interest to investigate the predictive ability of equations that model directional selection as a shift in the optimal values of a set of traits, under multivariate Gaussian selection. The standard equation for shifted optima (Lande, 1980a) is

$$\Delta\bar{\mathbf{Z}} = \mathbf{G}(\mathbf{W} + \mathbf{P})^{-1}(\theta - \bar{\mathbf{Z}}), \quad (3)$$

where \mathbf{W} is a symmetrical matrix, the diagonal elements being the strength of stabilizing selection acting on each trait (large values = weak selection) and the off-diagonal elements a measure of the strength of correlational selection. The superscript ‘ -1 ’ indicates matrix inversion, and θ is a column vector of trait optima. In modelling evolution with this equation it is assumed that an environmental change has brought about a change in θ , causing directional selection until the traits have evolved to their joint optima. Therefore, the strength of directional selection decrease as $\bar{\mathbf{Z}}$ approaches θ , but the strength of stabilizing selection (\mathbf{W} , the curvature of the fitness surface) remains constant. Hereafter, I will refer to (3) as ‘peak-shift’ selection, since the fitness optimum has been shifted to a new location. This should not be confused with the use of the term to describe the shift of a population’s genotype from one fitness peak to another in speciation through genetic drift.

Equation (3) still requires a number of assumptions, the most important of which are multivariate normality of genotypic and phenotypic trait values in both current and descendant populations, and constant \mathbf{G} and \mathbf{P} matrices. These assumptions will be violated to some extent in finite populations with finite numbers of loci. The consequences of such violations are studied here using stochastic simulations.

In this study I use simulated populations, subject to

the laws of Mendelian inheritance, to investigate the accuracy of (3), given various assumptions about the genetic details. The trajectories of the simulated populations’ trait means are compared with predictions from (3) that are based solely on information available at generation zero of directional selection. Changes in the variance, skew and kurtosis of the distribution of genotypic values are compared with those found or expected in previous models.

It is well established that the level of genetic variance that can be maintained by mutation-stabilizing selection balance (with or without genetic drift) depends on assumptions made about the distribution of mutational effects at each locus (Turelli, 1984). These assumptions have also been shown to be important in terms of the response expected when an equilibrium population is subjected to exponential directional selection (Burger, 1993) of the form

$$w(z) = e^{(sz)}, \quad (4)$$

where $w(z)$ is the mean fitness of individuals with phenotype z , and s is the strength of directional selection. Therefore, it follows that the accuracy of (3) should also depend on the genetic details of the starting population. This section briefly describes the three genetic models that will be simulated in this paper. For a thorough review, see Bulmer (1989).

Models of mutation–selection balance can be classified into two groups: those that assume the mutational (and therefore allelic) effects are continuously distributed, and those that assume effects are discrete and finite. Models of the first type are generally based on the continuum-of-alleles model of Crow & Kimura (1964). This assumes an effectively infinite number of alleles at each locus, producing a continuous distribution of effects. Lande (1975) extended this model to multiple loci, and developed a formula for the equilibrium variance now known as the Gaussian approximation to the continuum-of-alleles model. This assumes that mutational effects, α , are normally distributed at each locus, and that the variance of these effects is small compared with the standing per locus allelic variance ($\alpha^2 \ll \sigma_a^2$). The Gaussian approximation requires (Burger *et al.*, 1989)

$$\alpha^2 \leq 4\mu V_s, \quad (5)$$

where μ is the haploid per locus mutation rate, and $V_s = \omega^2$ (the strength of stabilizing selection on each character, equivalent to the diagonal elements of \mathbf{W} in equation 3) + σ_E^2 (the environmental variance).

Lande argued that under these conditions mutation–selection balance could maintain levels of genetic variance consistent with those seen in natural populations. Turelli (1984) showed that maintaining observed heritabilities under Lande’s assumptions would require per locus mutation rates far in excess of

what is usually thought to be realistic. He proposed an alternative formula for the equilibrium genetic variance, called the ‘house-of-cards’ (HC) or ‘rare allele’ approximation. This applies when the variance of mutational effects at each locus is large compared with the standing allelic variance ($\alpha^2 \gg \sigma_a^2$), and requires (Turelli, 1984)

$$\alpha^2 \geq 20\mu V_s. \quad (6)$$

This causes mutational effects to swamp the existing variance at each locus. The net effect is that most genetic variance is maintained by small numbers of mutant alleles at each locus, each of large effect. This tends to produce highly leptokurtic allelic distributions.

In the second type of model it is assumed that only a small number of allelic values are possible at each locus, with mutational effects limited to moving from one value to another. The first such models assumed two possible alleles (Latter, 1960; Bulmer, 1972, 1980). These have since been extended to include three (Turelli, 1984; Houle, 1989) and five (Slatkin, 1987*a*) alleles. Since the allelic values are fixed, traits are restricted to a finite range of genotypic values if the number of loci is finite. When multiple traits are considered, there are also limits on the divergence between traits. With three or more traits, these limits are determined by the eigenstructure of the **G** matrix rather than by the correlations between pairs of traits.

In this paper, three main types of initial population are simulated. The first two are continuum-of-alleles models that have either normal (= Gaussian) or leptokurtic (= HC) allelic distributions at equilibrium. Both of these assume normally distributed mutational effects, and will be referred to as ‘continuous effects’ populations. The third population type has two discrete values (−0.5 and 0.5) per allele, with equal forward and backward mutation rates, and will be referred to as ‘discrete effects’ populations. The response in populations with continuous leptokurtic mutational effects is also compared with the main continuous effects results.

2. The model

The main simulations consist of 4000 diploid individuals, with three genetically correlated traits. Sexes are separate but identical, and all data are averaged over the two sexes. Mating is random, and generations are non-overlapping. Populations are given 20000 generations to reach stabilizing selection–mutation–drift equilibrium (hereafter simply equilibrium) before the start of directional selection. The trait means (\bar{Z}) start and remain near their optimal values (θ) throughout this initial phase. Under most initial conditions the genetic variances decline steadily

for the first few thousand generations before reaching their equilibrium levels (generally before generation 10000). To simulate directional selection, the optimal value for trait 3 is shifted upwards by 10 phenotypic standard deviation units. All other conditions are identical in both the equilibrating and directional phases, for a given population type. For the directional phase of a given population type, five replicates of 1500 generations are run.

Although all the graphs shown are from only three initial populations, many others with different parameter values were simulated, to check the generality of the results, in terms of the effect of population size ($N = 4000$ or 400), magnitude of peak-shift and stabilizing selection intensity (**W**).

(i) Creating the population

Each individual has $L = 100$ unlinked loci. Populations with continuous allelic effects are initialized by assigning a random normal variate with mean zero and standard deviation 1 to each allele in each individual. Discrete effects populations are randomly assigned a −0.5 or 0.5 at each allele. Each of the three traits is controlled by $n = 50$ loci, randomly assigned from the 100 available per individual. The pleiotropic relationship between traits was produced by randomly assigning 50 ‘1’ s to each row of a 3 (traits) \times 100 (loci) matrix **B** (equivalent to Wagner’s (1989) **B** matrix). All other elements of **B** are assigned to ‘0’. A ‘1’ at element **B**_{*ij*} indicates that locus *j* contributes its allelic values to trait *i*. Columns with no ‘1’ s represent loci that are not assigned to any trait, and are therefore selectively neutral. All individuals use the same **B**, which is assumed to be constant. The same matrix is used for all simulations discussed in this paper.

(ii) Assigning trait values

The genotypic value of each trait in an individual is defined as the sum of all allelic values at all loci that code (via **B**) for that trait, and is therefore additive between and within loci. The expected average genotypic value for all traits is zero before directional selection. Phenotypic values equal the genotypic values, plus a random normal deviate with a mean of zero and a standard deviation set so as to produce an initial heritability of 0.5 for all traits. This heritability is in general higher than that present after the population has equilibrated. The environmental variance for each trait remains constant throughout selection. The environmental deviates added to each genotypic value within an individual are independent; thus the expected environmental covariance between traits is zero.

(iii) *Assigning survival probabilities and selecting parents*

Each offspring is assigned a survival probability, according to

$$w(\mathbf{Z}) = \exp(-0.5(\mathbf{Z}-\theta)^T \mathbf{W}^{-1}(\mathbf{Z}-\theta)) \quad (7)$$

(Lande, 1980*a*), where superscript ‘T’ indicates matrix transposition. For directional selection, θ for trait 3 (θ_3) is set to $+10\sigma_p$ (phenotypic standard deviation units). θ for all other traits remains at zero throughout the simulation. Equation (7) gives values between 0.0 and 1.0, and can be interpreted as the probability of survival. Therefore, selection is frequency-independent, since the fitness of each individual, and the population as a whole, is determined solely by its proximity to the optimal vector of phenotypes. From those individuals that survive viability selection in the previous generation, males and females are randomly assigned to monogamous pairs. Pairs are then randomly sampled with replacement, each time producing one offspring of each sex. Offspring consist of a random haploid complement of genes from each parent. Offspring phenotypes and fitnesses are assigned as above. This procedure is repeated until there are enough surviving offspring to replenish the original population. The number of offspring that have to be sampled in order to re-establish the initial population size is therefore a measure of the mean fitness of the population. This method of ‘viability’ selection (as used in Baatz & Wagner, 1997) produced results virtually identical to the alternative whereby parents were sampled (with replacement) each generation in proportion to their fitness (w) and produced offspring that automatically survived to stock the next generation (results not shown). All statistics and data are collected only from the surviving offspring.

Mutations are applied after selection, and do not affect that individual’s phenotype. Mutational effects are added to the value of pre-existing alleles. The formula for the house-of-cards (HC) approximation for the equilibrium genetic variance assumes that mutational effects are ‘essentially independent’ (Turelli, 1984) of pre-existing allelic values. However, this assumption is required in order to simplify the mathematics, and is not intended as a statement concerning the actual effect of mutations in real populations. Therefore, HC populations in this paper have mutational effects of relatively high variance, and low mutation rates (compared with the Gaussian populations), but do not implement the simplification required for Turelli’s approximation.

(iv) *Constants, and parameter estimates*

\mathbf{G} and \mathbf{P} are estimated at generation zero of directional selection, from the genotypic and phenotypic values

of all individuals. The diagonal elements of \mathbf{W} are set to 15 times the environmental variance of each corresponding trait. This is a value within the range of experimental estimates (Johnson, 1976; Turelli, 1984). The off-diagonal elements of \mathbf{W} are set to zero. For the continuous effects models, genetic variance (V_G) = $2n\sigma_a^2 \cong 100$, assuming global linkage equilibrium. Since the heritability of each trait is set at 0.5, V_E = the initial V_G . Mutational heritability (h_M^2), defined as the mutational variance $V_M (= 2n\mu\alpha^2)/V_E$, is set to 0.001, a value consistent with empirical findings (Lynch, 1988; Houle *et al.*, 1996). Given $V_E = 100$ and $2n = 100$, $\mu\alpha^2$ must equal 0.001 to produce this value (note that V_E is not set to the conventional 1.0). The Gaussian simulations use $\mu = 0.001$ and $\alpha^2 = 1.0$. While this violates $\alpha^2 \ll \sigma_a^2$, it does create Gaussian allelic distributions at equilibrium (confirmed by simulation). To simultaneously satisfy $h_M^2 = 0.001$, $\alpha^2 \ll \sigma_a^2$ and $n = 50$ would require mutation rates on the order of 10^{-2} . The HC simulations use $\mu = 0.0001$ and $\alpha^2 = 10.0$. For populations with discrete allelic effects, a μ of 0.0001 is used as the rate at which each allele changes from 0.5 to -0.5 , or vice versa. In all populations, the number of mutations per generation is drawn from a Poisson distribution with a mean of $2L\mu N$.

For populations with leptokurtic mutational effects, the reflected gamma distribution is used, where the density function of mutational effects α (randomly assigned either a positive or negative sign) is given by

$$k^b e^{-k\alpha} \alpha^{b-1} / \Gamma(b), \quad (8)$$

where Γ is the gamma function, b is a shape parameter and k is a scaling parameter adjusted so as to produce a mutational variance of 0.001 V_E as in the above simulations with normally distributed mutational effects. The value of b is set to 0.5 to produce a highly leptokurtic distribution, as in several previous simulation studies (e.g. Keightley & Hill, 1989; Burger & Lande, 1994).

3. Results

Fig. 1 shows the observed and predicted trajectories of the trait means for the different models. The prediction for all three traits is very accurate for the Gaussian population (Fig. 1*A*). The discrepancy between the average observed and predicted values is never greater than $0.3\sigma_p$ for any generation. With a population size of 400 (results not shown) the predictions were nearly as good (maximum discrepancy = $0.6\sigma_p$). The predictions for the HC population (Fig. 1*B*) are much less accurate, with discrepancies as large as $3.7\sigma_p$. In this population, (3) underestimates the rate of response and correlated response, while overestimating the time required to reach equilibrium. Predictions for $N = 400$ HC population underestimated the true re-

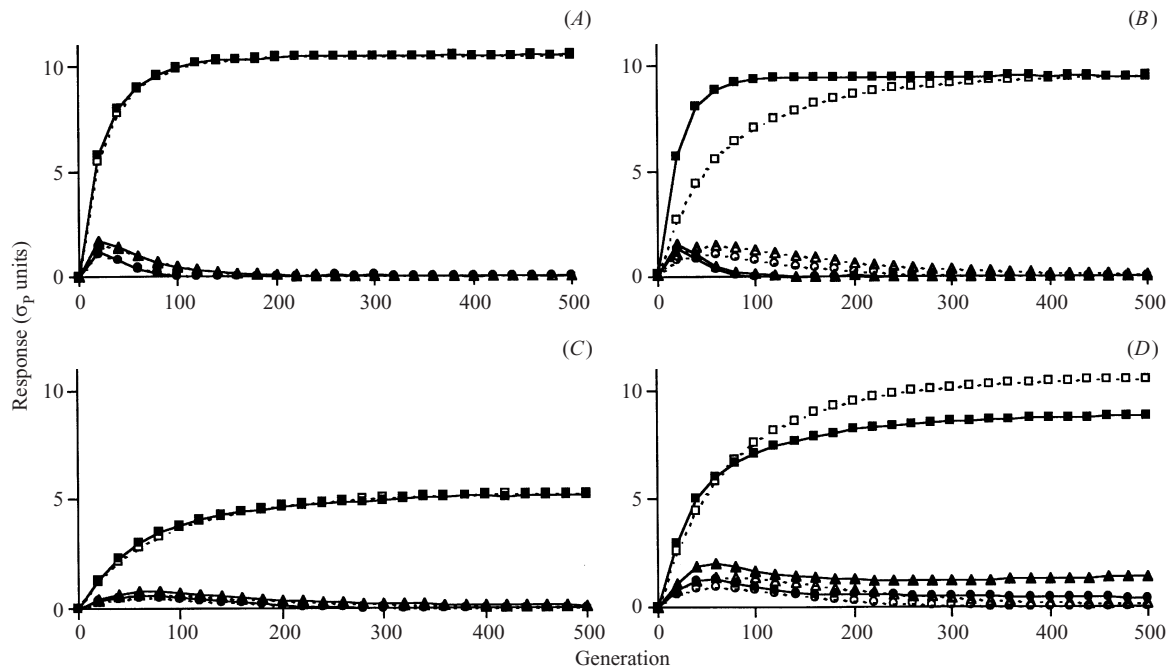


Fig. 1. Response of trait means to shifted-optima selection on trait 3. Units are phenotypic standard deviations. (A) Gaussian conditions. (B) House-of-cards conditions. (C), (D) Biallelic loci. All peak-shifts are for $+10\sigma_p$, except (C) which is for $+5$. Filled symbols, continuous lines: simulation results. Open symbols, dashed lines: predictions from (3). Trait 1, triangles; trait 2, circles; trait 3, squares. Heritabilities (averaged over traits) of the starting populations were 0.44, 0.14, 0.16 and 0.16 for (A)–(D) respectively. All graphs in this paper are based on the average of five replicate runs.

sponse by $2.7\sigma_p$. When the starting population from Fig. 1B was given a θ_3 shift of $+5\sigma_p$ instead of $+10$, the results were qualitatively similar, with average discrepancies as large as $1.4\sigma_p$.

The quality of predictions from biallelic models depends on the relationship between the peak-shift and the selection limit (see Section 4). Fig. 1C shows that when the peak-shift ($5\sigma_p$ in this case) is within the limit, predictions are good, and the average discrepancy was never larger than $+0.2\sigma_p$. Average discrepancies in the 400 population size (results not shown) approached $+0.3\sigma_p$. In Fig. 1D, a peak-shift of $10\sigma_p$, as in Fig. 1A and B, exceeds the limit, resulting in suboptimal evolutionary equilibria. Population size and mutation rate have no effect on this limit.

For all three types of population, running the directional phase of selection without mutation has virtually no effect on the trajectory of the means. Therefore, for the continuous effects populations, there is enough standing variance to easily move $10\sigma_p$. For the biallelic population, mutation rate has little effect on anything but the equilibrium variance (see Section 4).

Fig. 2 shows the changes in several genetic parameters caused by directional selection, for the continuous effects models of Fig. 1A and B. In the Gaussian population, genotypic variances increase by 15–25%, peaking at generation 80–90 (Fig. 2A). The variances of traits 1 and 2 change more than that of

trait 3, despite the means being displaced far less. In the HC population (Fig. 2b) the variance peaks at generations 30–80, with a 6-fold increase in trait 3 and a 4-fold increase in traits 1 and 2. When the HC population was run at $N = 400$, variance still increased by up to 4 times. With $N = 400$ and $V_s = 60$ (rather than 16 as in the main simulations), variance increased by a factor of 1.8, although there was not a noticeable increase until about generation 20.

The skew and kurtosis of the Gaussian population's trait genotypic values remain near the values of normal distributions (0.0 and 3.0 respectively). In the HC population the skew for all traits is initially near 0.0. The skew in traits 1 and 2 remains near 0 except for the first 15–25 generations, when there is a positive skew of up to ≈ 0.3 . The skew for trait 3 reaches a higher peak (≈ 0.4), but continues to decline for hundreds of generations. Kurtosis was high in the starting population (≈ 3.4) but was quickly driven to normal levels, and then steadily increased from generation 300 onward. It eventually returned to pre-directional selection levels. These figures show how the genetic characteristics of the populations continue to evolve long after the trait means have reached an apparent equilibrium.

Fig. 3 shows the genetic changes in the biallelic populations from Fig. 1C and D. As with the continuous effects models, both populations initially show an increase in genetic variance. Notice that in Fig. 3B the population maintains variance for all

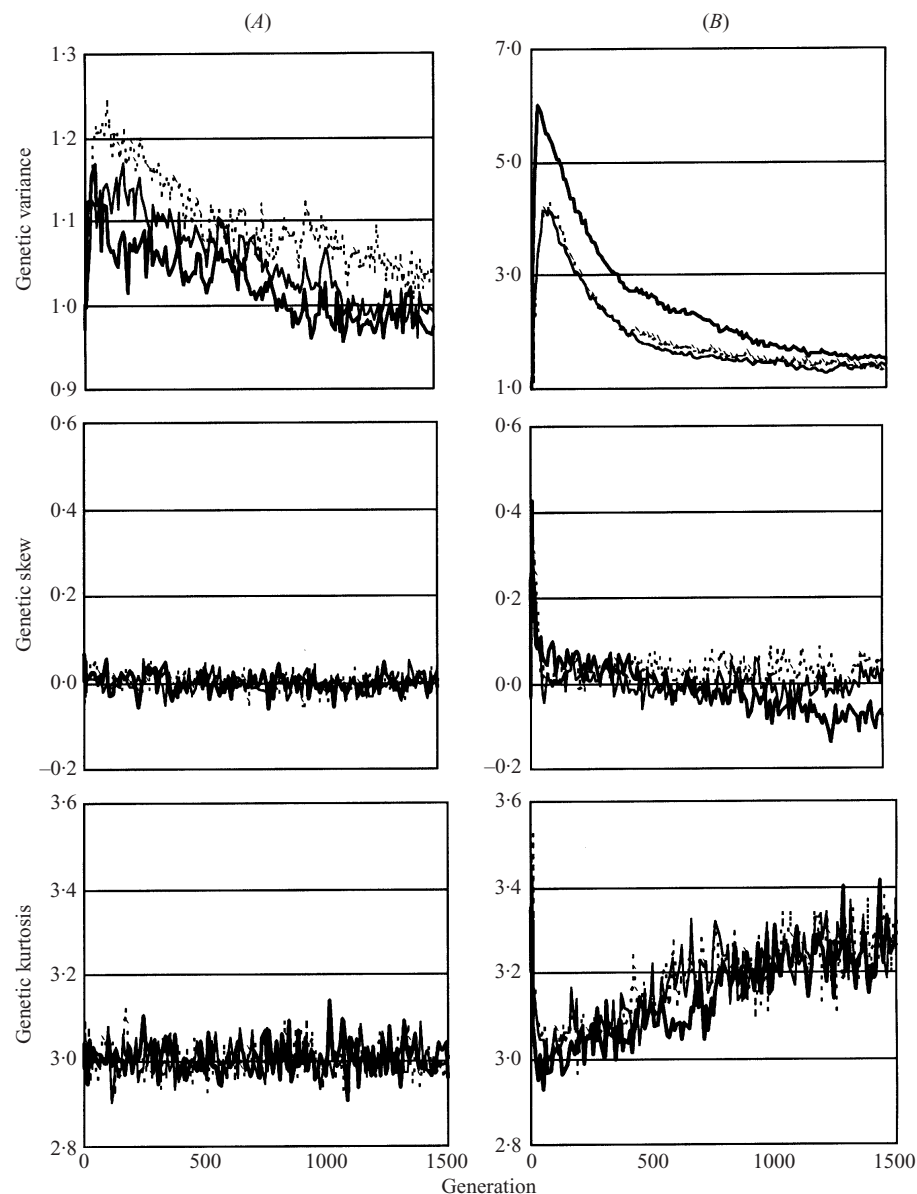


Fig. 2. Genetic variances, skews and kurtoses for (A) Gaussian, and (B) house-of-cards populations corresponding to Fig. 1A and B respectively. Genetic variances are standardized to the level in generation zero. Note that the scale is different for the two variance graphs. Trait 1, thin dotted line; trait 2, thin continuous line; trait 3, thick continuous line.

traits, despite the trait means being at a suboptimal equilibrium. The normality of the starting population is a consequence of the symmetry of the allelic effects (-0.5 and 0.5) about the optimum (0.0). This guarantees that directional selection will produce skew and positive kurtosis proportional to the peak-shift, given the restrictions on mutational effects.

In Fig. 4 the effect of directional selection on genetic correlations in the four populations is shown. Only in the Gaussian population do the correlations remain relatively constant (Fig. 4A). In HC populations (Fig. 4B) the patterns of change are irregular and are apparently very dependent on the exact starting conditions and the nature of the peak-shift. In the

biallelic population (Figs 4C, D) correlations increase as loci unique to trait 3 increase the frequency of their high alleles. Fig. 4D shows that pairwise correlations of less than 1.0 do not guarantee that traits will reach their optima in biallelic models if there are more than two traits in the system. This effect has previously been noted in algebraic models of multitrait systems (Slatkin, 1987b; Charlesworth, 1990).

Textbook descriptions of changes in the genetic correlation during directional selection are usually based on the biallelic model, as is appropriate for small, laboratory populations that are often derived from crosses between lines. The changes expected in large continuum-of-alleles populations (Fig. 4A, B)

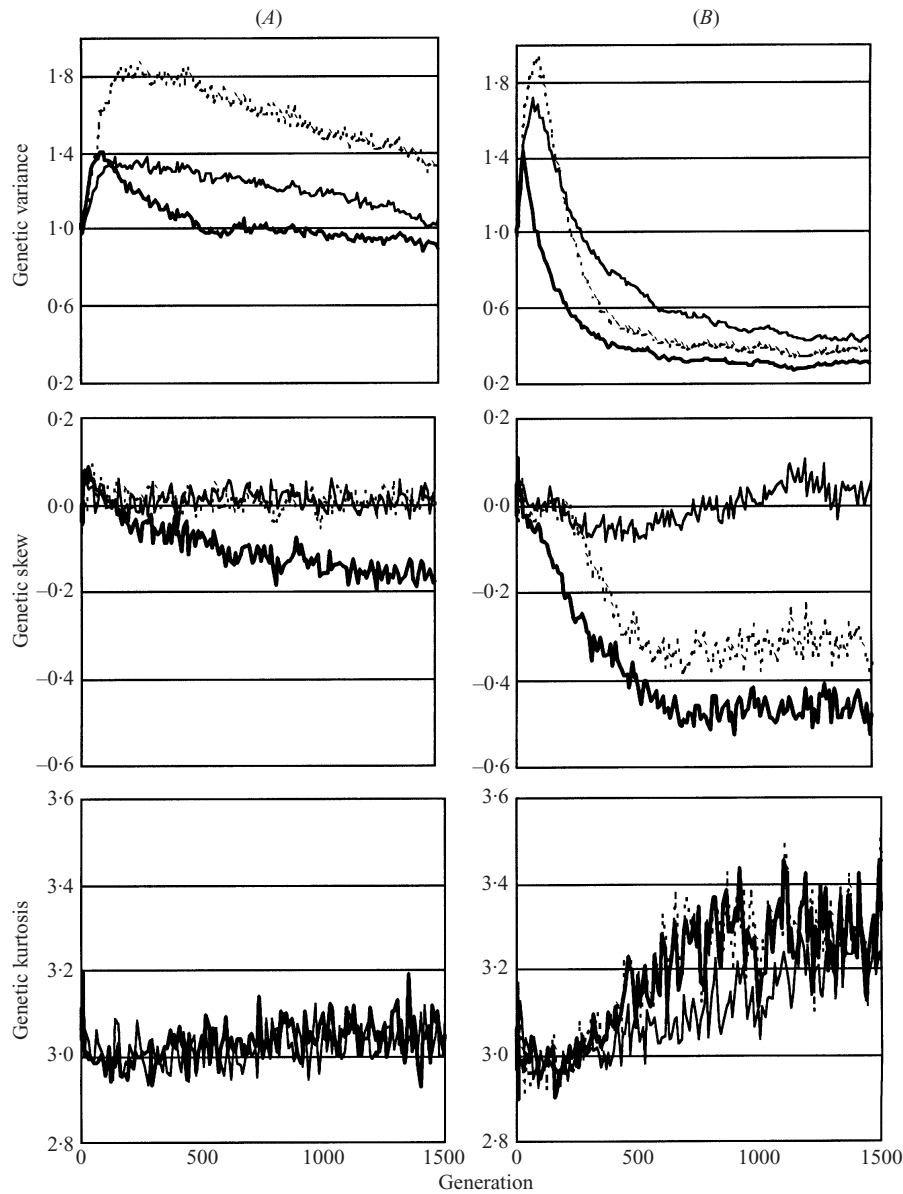


Fig. 3. Genetic variances, skews and kurtoses for biallelic populations where the selective optima θ is either (A) within or (B) beyond the selection limit. Genetic variances are standardized to the level in generation zero. (A) and (B) correspond to the populations from Figs. 1 C and D respectively. Symbols as in Fig. 2.

are far less intuitive, due to the presence of continuously distributed allelic (mutational) effects.

The median allelic skew and kurtosis from the HC population are shown in Fig. 5, where loci have been classified according to the combination of traits they control. There are eight classes (0, 1, 2, 3, 1 + 2, 1 + 3, 2 + 3, 1 + 2 + 3), containing 19, 7, 11, 14, 13, 10, 6 and 20 loci respectively. The 19 neutral loci of class '0' are not shown in this figure, as they do not respond in any directed manner to the directional selection encountered here. As directional selection starts and rare alleles with large positive effect on trait 3 increase in frequency, the skew for the four classes that include trait 3 moves to a high level. (Note that the exact value of the skew in the equilibrium population is highly

variable between generations, so these classes may start with almost any value.) The other non-neutral classes generate skew in the opposite direction at the point where the net selective forces start favouring smaller values of traits 1 and 2 (compare with Fig. 1 B). This effect of having both directions of skew in different subsets of genes will tend to produce genetic distributions that are less skewed than their underlying allelic effects. This is important because standard Gaussian predictions such as (3) assume that genetic variance remains constant on directional selection. Barton & Turelli (1987) have shown that this is a consequence of assuming that there is no allelic skew.

At the post-directional selection equilibrium, negative skew was highly significant in classes 3 (-1.6) and

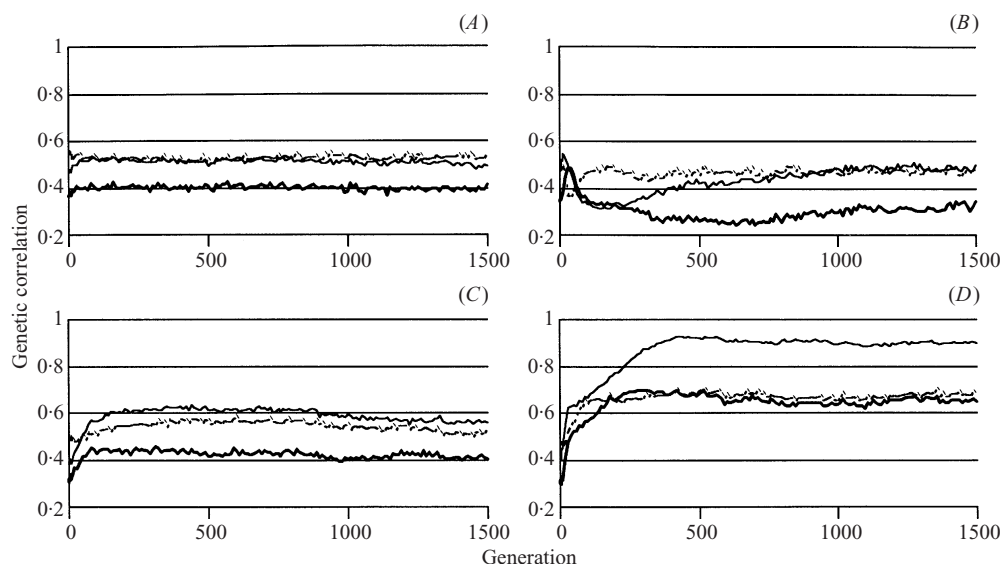


Fig. 4. Changes in genetic correlations caused by peak-shift selection. (A) Gaussian conditions. (B) House-of-cards conditions. (C) Biallelic loci. Peak-shift within limit. (D) Biallelic loci. Peak-shift beyond the selection limit. (A)–(D) correspond to the trait responses with the same letter in Fig. 1. Correlation (r_{ij}) between traits i and j : r_{12} , thin dotted line; r_{13} , thin continuous line; r_{23} , thick continuous line.

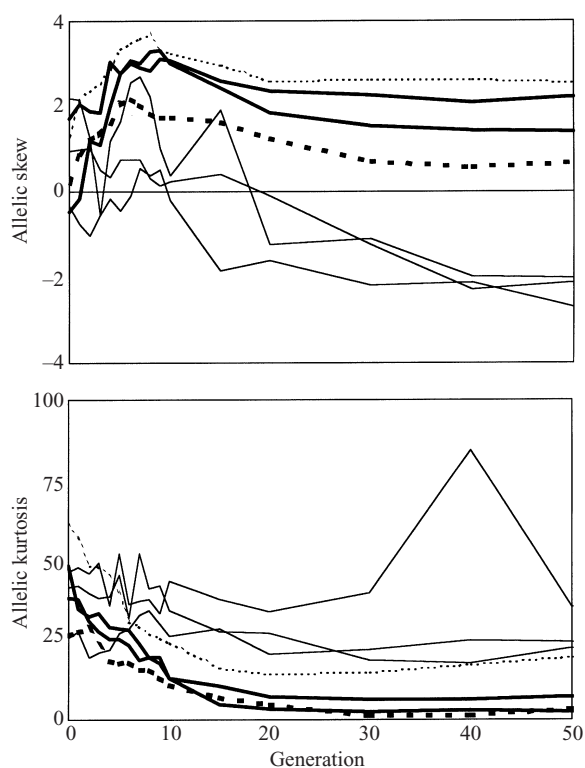


Fig. 5. Changes in median allelic skew and kurtosis for the HC population of Fig. 1B. Loci are classified according to the combinations of traits they control, as determined by the **B** matrix. Loci controlling traits: 1, 1+2, 2, thin continuous line; 1+2+3, thin dotted line; 1+3, 2+3, thick continuous line; 3 thick dotted line.

1+3 (−1.03) (based on the median skew per class per generation, averaged over generations 2000–5000, measured every 50 generations to reduce autocor-

relation (Keightley & Hill, 1988; Burger *et al.*, 1989)). Thus, these two classes account for most of the negative skew seen in the genotypic distribution of trait 3 in the same simulations (Fig. 2B). Although the variability amongst replicates is very small for the predicted and observed trait means, it increases rapidly with increasing moments of the genotypic distribution. As an example, two other sets of five replicates under the same conditions produced (a) a long-term depression in the skew for trait 2, and (b) no long-term depressions. It is likely that the populations can move between different equilibrium states (as in Barton, 1986), which can have a large influence on the behaviour of the higher moments but less on the variance and, especially, the means. However, on the introduction of directional selection, all replicate sets behaved qualitatively as described above for Fig. 5.

The kurtosis of the trait 3 classes declines rapidly on directional selection, again due to selection for rare alleles. The decline in kurtosis for the other classes is much weaker, and is generated by the same processes that produce negative skew.

The continuum-of-alleles simulations with leptokurtic mutational effects produced the expected results: greater allelic leptokurtosis, and therefore a greater increase in variance in response to directional selection than populations with normally distributed mutational effects (results not shown). A mutation rate of 0.001 produced a maximum average deviation between simulation and equation that was approximately 5 times as large, and an increase in variance that was twice as large, as in the population of Fig. 1A. Lowering the mutation rate to 0.0001 (at a fixed mutational heritability) resulted in 4-fold increase in

genetic variance over that of the population in Fig. 1B, but little difference in the accuracy of trait mean predictions.

4. Discussion

This paper attempts to answer a relatively straightforward question: If a change in environmental conditions causes selection for a new value of a single trait, can Lande's shifted optima equation be expected to accurately predict the trajectory by which this trait, and any others correlated with it, will evolve? The answer, like that to the question of how much variation can be maintained through mutation–selection balance, depends crucially on the nature of mutational effects. As almost nothing is known about the frequency, magnitude or distribution of mutations at typical polygenic trait loci, it is not possible to assess the predictive accuracy of the equation. All that can be done, at least until more empirical data are available, is to show what conditions are required for making accurate predictions and to describe, qualitatively, the nature of the errors produced when these conditions are not met. Like other models, this simulation makes numerous simplifying and unrealistic assumptions. For instance, dominance, trait value epistasis and physical linkage are absent, and fitness is determined completely by multivariate Gaussian selection on the trait values. However, the simulation is not primarily intended as a model of how evolution works. Rather, it makes assumptions consistent with those from standard quantitative genetic theory, and asks how the unavoidable complications associated with finite populations and finite numbers of loci are likely to affect the predictions of a specific equation.

The main results from this paper can be summarized as follows:

(1) If allelic distributions are approximately Gaussian, (3) can produce very accurate predictions, based only on information gathered at generation zero of directional selection. These predictions were accurate despite the fact that the genetic variances changed by more than 20% during the directional selection phase. Such populations start with little genetic skew or kurtosis, and this changes little with directional selection. Thus, under these conditions, evolutionary trajectories may be understood in terms of the simple parameters of (3).

(2) Under HC conditions, the predictions can be very inaccurate. Equation (3) underestimates the rate of response and correlated response, and overestimates the time it takes for the traits to get to their equilibrium values. In most of the populations tested, including that in Fig. 1B, correlated responses were also of greater magnitude than predicted, sometimes mark-

edly so. Directional selection can result in very large increases in genetic variance as initially rare alleles increase in frequency.

(3) If mutational effects in continuum-of-alleles populations are leptokurtically distributed, directional selection will cause larger increases in genetic variance for any given mutational heritability. This causes the trait means to respond more quickly than predicted, even in high mutation rate (= smaller mutational effect) populations.

(4) For biallelic models, (3) makes good predictions as long as the peak-shift does not require trait mean equilibrium values that are more divergent than can be accommodated by the genetic architecture of the 'species' (see below). Predictions become progressively worse as the optimum exceeds the selection limit. In such cases, suboptimal equilibria will be reached, despite the presence of genetic variation in each individual trait.

(5) For many of the parameter combinations used to test the generality of the main results, peak shifts of $10\sigma_P$ resulted in genetic variances and covariances at the new equilibrium that were remarkably close to those seen in the population before directional selection. Therefore, interpretation of the role of drift versus selection in shaping the **G** matrix should be made with caution. It may be that the changes in **G** brought about by selection to new optima are often temporary, even in relatively small populations. If this is the case, the changes in **G** found in short-term laboratory selection experiments may be fundamentally different from those expected between populations or closely related species that have been experiencing different selection regimes for long periods of time.

Peak-shift models of the sort considered here have received relatively little theoretical attention, and most of this has dealt with very different types of questions. For instance, conservation biology issues have motivated research on the ability of a population to keep up with an optimum that is changing either gradually or randomly (Lynch & Lande, 1993; Burger & Lande, 1994; Burger & Lynch, 1995). Charlesworth (1993) considered an optimum that could also change cyclically, to study the effect of directional selection on the evolution of sex and recombination. Each of the above studies used a single trait, and did not use the univariate form of (3) to describe the evolution of the mean phenotype. Zeng (1988) used a modification of (3) to look at the effects of correlational selection on patterns of long-term correlated response in infinite populations. Other papers have considered the evolution of two traits, one under stabilizing and the other under exponential directional selection (e.g. Burger, 1986; Wagner, 1988; Baatz & Wagner, 1997). Barton & Turelli (1987) used allelic recursion equations to simulate peak-shift selection in a single-trait system,

using moment-generating functions to make predictions for the mean and higher moments.

This is the first paper to test the predictions of (3) by simulation. Although more general predictive equations are available (Barton & Turelli, 1987; Burger, 1993), they require detailed information about higher genetic moments or cumulants that are generally unobtainable. In addition, none of these have been extended to multivariate systems. Equation (2) and its descendants, including (3), are popular because they attempt to predict, or at least explain, evolution in terms of a small number of relatively familiar parameters that can, in principle, be estimated.

(i) *Causes of prediction error*

The rapid increase in genetic variance seen in the HC population (Fig. 2*B*) causes the means to respond to selection far more rapidly than predicted by (3). This increase in variance as a result of directional selection has been shown previously in single-trait simulations by Barton & Turelli (1987; peak-shift), Keightley & Hill (1989; pure directional [$w = Z$]), Burger (1993; exponential) and Burger & Lande (1994; shifting optimum). The increase is largely due to selection for rare alleles that initially contribute little to the variance. As these alleles increase in frequency they contribute more to the variance, and soon cause the mean to increase at an accelerating rate (Barton & Turelli, 1987). For a fixed mutational variance, lowering the mutation rate will result in equilibrium populations that have less genetic variance but higher allelic skew and kurtosis. The accelerated response to the mean is not simply a consequence of the lower equilibrium heritability (see caption for Fig. 1) in HC populations. Increasing this heritability to Gaussian population levels, either by decreasing the strength of stabilizing selection or increasing the total (L) and trait-specific (n) number of loci, did reduce the amount by which the variance increased during directional selection. However, the quality of the predictions was only slightly improved, with the discrepancy between observed and predicted response remaining roughly an order of magnitude greater than in the Gaussian populations (results not shown).

In using (3) it is assumed that the distribution of genotypic values is, and will continue to be, multivariate normal, and therefore that the dynamics of trait mean evolution can be described completely in terms of the mean and variance. HC populations have far more evolutionary potential, in terms of rate of response, than Gaussian populations with the same variance. Therefore, heritability is not an accurate predictive statistic in such populations.

An increase in genetic variance is seldom seen in artificial selection experiments, which would seem to

be evidence against the generality of HC conditions (discussed in Keightley & Hill, 1989). Burger (1993) concluded that a significant increase in variance is unlikely if N_e is less than about 500. This figure was based on typical parameter estimates for the HC model, combined with the fact that genetic variance in his model converged to the mutation–drift equilibrium level under a particular form of exponential selection. For the peak-shift selection used in the present simulation, HC populations with an N of 400 ($N_e \cong 300$) still had a 4-fold increase in variance. When the intensity of stabilizing selection was decreased ($N = 400$, $V_s = 60$), there was a 1.8-fold increase in variance. Therefore, Burger's conclusion may not extend to all forms of directional selection. However, the N_e in selection experiments is typically much smaller than 300. In addition, we know nothing about how existing univariate estimates of stabilizing selection intensity should be adjusted when considering multivariate systems. Therefore, failure to detect increased variance in selection experiments probably cannot be taken as evidence against the HC model.

(ii) *Selection limits in models with discrete allelic effects*

Discrete effects models have been used extensively in quantitative genetics (e.g. Latter, 1960; Bulmer, 1972, 1980; Barton, 1986, 1989; Turelli & Barton, 1990). They may be interpreted either as a realistic representation of the allelic effects for at least some loci, or as a method of simplifying the analysis of continuous effects models (Houle, 1989). In the latter case, results such as those in Fig. 1*C* may lead to unwarranted confidence in the predictive ability of standard theory – such as (3) – if HC conditions are the norm. The lack of rare alleles of large effect in the biallelic simulation has produced a result consistent with (3) because the behaviour of the variance is more similar to that seen in the Gaussian than in the HC population. Here, trying to extend the results of the ‘simplifying’ model to the situation with continuous effects would bias the conclusions.

Alternatively, if discrete effects models are taken as a realistic representation of allelic effects, the limit problem deserves some consideration, at least when modelling the evolution of trait means. To see why the limit occurs, consider a system of 20 genes with free recombination, where loci 1–12 and 9–20 control traits 1 and 2 respectively. If the two traits are selected in opposite directions, the correlation between traits will approach 1.0 as the loci unique to each trait fix in the appropriate direction. Genetic variance for both traits remains, however, since loci 9–12 will still be segregating. The amount of divergence between traits is a function of the number of loci unique to each trait,

and their allelic effects. The same situation exists for systems of three or more traits, except that pairwise correlations at the limit no longer have to be 1.0 (e.g. Fig. 4D), since each trait will generally share segregating loci with more than one other trait. At a suboptimal limit, as in Fig. 1D, the genotypic fitness of the population cannot increase, since mutations cannot improve upon the alleles that are already present. Therefore, mutation rate has no effect on the limit. In Fig. 1D, the eigenvalue corresponding to an increase in trait 3 and a decrease in the other traits is near zero, so the **G** matrix is nearly singular for that direction of response. It is not completely singular because mutation continues to produce genotypes that are slightly less fit than those at the limit.

If the alleles at each locus are typically restricted to a finite number of values, the simulations suggest that the situation found in Fig. 1D might be common, since all it requires is a large peak-shift (= prolonged directional selection). This situation would be characterized by a lack of response in a population, despite the presence of genetic variance for each trait, genetic correlations less than 1.0, and non-zero values for the coefficients of the phenotypic selection gradient (measured as in Lande & Arnold, 1983). These non-zero coefficients exist because environmental variance can produce phenotypes more fit than those at the genetic limit, but this fitness difference is not heritable. There are in fact several examples of such a lack of response in natural populations (e.g. Price *et al.*, 1988; Alatalo *et al.*, 1990; van Tienderen & de Jong, 1994; Weis, 1996), although in most cases the authors have provided compelling evidence for simpler explanations. These include the effect of missing traits on the analysis, and non-heritable traits influencing the focal trait(s) and fitness through different pathways (Price *et al.*, 1988; Rausher, 1992).

It should be noted that in discrete effects populations with allele frequencies near fixation (as when directional selection has driven the population to a suboptimal selection limit), subsequent selection in the direction of the rare allele causes a pattern of response similar to that seen in HC populations (results not shown). Genetic variance increases as the rare alleles become more common, and the trait means respond to selection more rapidly than predicted by (3). However, the response is very slow compared with HC models, due to much lower initial heritabilities.

Although this paper has examined the predictive ability of only one equation, a large number of other theoretical models are based on the same underlying assumptions, stemming from the use of (1). These include models for the evolution of sexual size dimorphism (Lande, 1980b), phenotypic plasticity (Via & Lande, 1985), maternal effects (Kirkpatrick & Lande, 1989) and epigenetic effects (Atchley & Hall,

1991), to name but a few. If ‘house-of-cards’ assumptions are more realistic than those of the Gaussian model, some of the conclusions of these models are likely to be at least quantitatively inaccurate. For instance, in Lande’s (1980b) paper on the evolution of sexual size dimorphism he models the situation where sexual selection for increased values of a trait in males causes a temporary, maladaptive increase in the homologous trait in females. Given typical genetic correlations between the sexes, he concludes that the time for the traits in each sex to reach their equilibrium values may be on the order of millions of generations. From the simulation results in this paper, HC conditions might be expected to reduce that time substantially.

Given current estimates of mutation rates and mutational heritabilities, it is likely that allelic effects are leptokurtically distributed. Therefore, directional selection in moderate to large-sized populations is likely to cause an increase in genetic variance. Because of this, Gaussian-based quantitative genetic models will often underestimate the rate at which trait means respond to selection. In models involving stabilizing selection, this will result in overestimates of the time required for populations to reach equilibrium.

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