Introduction

History

Darwin's theory, combined with practical application, inspired biometry, which developed into *quantitative genetics* (Galton, Weldon, Pearson,…)
Rediscovery of Mendel's work in 1900 led to fierce argument between the new Mendelian genetics and biometry, reconciled by population genetics in 1920s
Nevertheless, quantitative genetics developed largely independently through to the present

Alternative views of evolution

In QG, we see ubiquitous additive genetic (co)variance, V_a or G; traits can always evolve to their optimum

- rates of trait evolution are determined by how selection changes through time

Under the 'classical' view of population genetics, there is one optimal genotype

- variation is either neutral, due to deleterious mutation, or (rarely) to transient adaptation
- evolution consists of successive sweeps, variation within populations being uninteresting

In contrast, under the 'balance' view, variation is maintained by balancing selection, and allows rapid response to changing conditions

Difficulties

- quantitative genetic variation for very many traits implies loss of fitness
- under the classical view, there is little heritable fitness variance; how can sex and recombination be maintained?
- under the balance view, genetic variance should depend on idiosyncratic fluctuating selection - yet it seems ubiquitous

Outline

What is the relation between quantitative and population genetics?

Directional selection

Infinitesimal model at phenotypic and genetic levels
Limits to the response to directional selection

Stabilising selection

Maintenance of variation by mutation
Response to a sudden change in optimum

Directional selection

Infinitesimal model

Definition

See Galton (*Nature,* 1877), Barton, Etheridge & Veber (*TPB,* 2017).

> '' I was certainly astonished to find the family variability of the produce of the little seeds to be equal to that of the big ones, but so it was, and I thankfully accept the fact, for if it had been otherwise, I cannot imagine, from theoretical considerations, how the problem could be solved''
> (Galton, 1877)

Each individual has a *breeding value,* z_i, defined as twice the deviation of the offspring mean, when crossed at random
Offspring from a cross between two parents, z_1, z_2, have breeding values distributed as a Gaussian, with mean $\frac{z_1+z_2}{2}$, and variance V_0
Crucially, $V_0$is *independent* of the parents' values.

With random mating, a population tends towards a Gaussian with constant variance $V_A = 2\,V_0$.

Extensions

The within-family variance, V_0, is released by recombination.
If the parents are related, then this variance is reduced to $V_0(1 - F)$, where F is the probability of identity by descent of the genes that are shuffled in meiosis.
In a population of effective size N_e, V_o decreases by a factor $\left(1 - \frac{1}{2\,N_e}\right)$ per generation.
F is derived from the pedigree, and takes into account inbreeding, population structure...

V_A increases by V_m in each generation due to mutation -> $V_m \approx 10^{-3}\,V_e$; in a mutation-drift balance, $V_A \to 2\,N_e\,V_m$

Allele frequencies

Assume two alleles per locus, labelled $X_i = 0$ or 1; allele frequency is $p_i = \mathbb{E}[X_i]$.
For an additive trait in diploids, define $z = \sum_{=1}^{n} \alpha_i(X_i + X_i^*) + \epsilon$, where ϵ is a non-genetic ("environmental") component with variance V_E
The mean and the additive genetic are $\bar{z} = \sum_{=1}^{n} 2\,\alpha_i\,p_i$, $V_A = \sum_i 2\,\alpha_i^2\,p_i\,q_i$

If there are very many loci ($n >> 1$), then for a given V_A, $\alpha_i \sim 1 \Big/ \sqrt{n}$.

What is the variance amongst offspring? Variation is due to heterozygosity in the parents:

- probability $2 \times 2\,pq \times (1 - 2\,pq)$ that one locus is heterozygous ⇒ variance $\frac{\alpha^2}{4}$

= probability $(2pq)^2$ that both are heterozygous $\Rightarrow \frac{\alpha^2}{2}$

Overall, the expected variance in BV between offspring contributed by locus $i \sim \alpha^2 pq$

Overall, $\sum_i \alpha_i^2 p_i q_i = V_0 = \frac{V_A}{2}$ is released by segregation of heterozygous alleles in meiosis

Selection: change in mean $\Delta \bar{z} = \beta V_A$

Suppose that there is a selection gradient $\beta = \frac{d \log(\bar{W})}{d \bar{z}}$, so that the selection coefficient on an allele with effect α is $\beta\alpha$.

Then $\Delta p_i = \beta \alpha p_i q_i$, and so $\Delta \bar{z} = \sum_{i=1}^{n} 2 \alpha_i \Delta p_i = \sum_{i=1}^{n} 2 \beta \alpha_i^2 p_i q_i = \beta V_A$

The *response to selection* (i.e., $\Delta \bar{z}$) depends on allele frequencies and effects *only* through V_A

Selection: change in V_A is small

$\Delta V_A = 2 \sum_i \alpha_i^2 \Delta(p_i q_i) \approx 2 \sum_i \alpha_i^2 (q_i - p_i) \Delta p_i = 2 \beta \sum_i \alpha_i^3 (q_i - p_i) p_i q_i = \beta S$ where S is the third moment, or *skew* of the distribution of additive effects.

The skew, and hence ΔV_A, is typically *small*: $\triangle V_A \sim \beta V_A \mathbb{E}^*[\alpha_i (q_i - p_i)]$ where $\mathbb{E}^*$ is an expectation weighted by the genetic variance.

So, selection hardly changes V_A - both because α is small $\left(\sim 1/\sqrt{n}\right)$, and because $(q - p)$ averages ~0

The distribution changes mainly because of *linkage disequilibrium*

Even under the infinitesimal model, selection can make large changes to the distribution.

The figure shows the effects of disruptive selection (fitness $W[x]$ given by the dashed line), followed by random mating and reproduction:

The variance evolves as $V_{A,t+1} = \frac{1}{2} V_{A,t} + V_0$, which quickly converges to $V_A = 2 V_0$

These changes are due to *linkage disequilibrium* (LD), and are therefore *transient*.

LD is defined as $D_{i,j} = \text{cov}(X_i, X_j) = \mathbb{E}[(X_i - p_i)(X_j - p_j)]$

Defining $\zeta_i = X_i - p_i$, $V_A = \mathbb{E}\left[\sum_{i,j} \alpha_i(\zeta_i + \zeta_i^*)\, \alpha_j(\zeta_j + \zeta_j^*)\right]$
Assuming random mating, and symmetry between the sexes, $V_A = 2\sum_{i,j} \alpha_i\, \alpha_j\, \mathbb{E}\left[\zeta_i\, \zeta_j\right]$
This separates into the *genic* and the *LD* components: $V_A = 2\sum_i \alpha_i^2\, p_i\, q_i + 2\sum_{i\neq j} \alpha_i\, \alpha_j\, D_{i,j}$

Dominance and epistasis

The infinitesimal model is easiest to understand as the limit of an additive model, with a large # of loci.
However, the concept extends to allow dominance and epistasis, in which case we follow the evolution of additive and non-additive components of phenotype.
This gets complicated - but there is still an infinitesimal limit in which the variances within families are independent of the parent's values.

The figure shows an example with 1000 loci, each with complete dominance;
$V_A = 0.269$, $V_D = 0.063$, and inbreeding depression is i=-0.531; 30 individuals evolve for 50 generations, with no selection. The top row shows one replicate, and the bottom row, the mean of 300 replicates. Black, blue, red correspond to G, A, D; in the right column, solid lines show the total variance (including LD), and dashed lines, the *genic* components, which match predictions from the infinitesimal model. The purple lines at right show cov(A, D). From Barton, Etheridge, Véber (*Genetics*, 2023).

Limits to selection

The infinitesimal model: Robertson (1960)

Random sampling from a population of $2N$ genes causes var(Δp) = $\frac{pq}{2N}$, and reduces expected heterozygosity by a factor $\left(1 - \frac{1}{2N_e}\right)$.

Since the genetic variance is $V_A = 2\sum_i \alpha_i^2 p_i q_i$, V_A decreases by a factor $\left(1 - \frac{1}{2N_e}\right)$.

With a selection gradient β, the change in mean in the initial generation (the *response*) is $R_0 = \beta V_{A,0}$, and the *total* change in mean is $R_\infty = \beta V_{A,0} \sum_{t=0}^{\infty}\left(1 - \frac{1}{2N_e}\right)^t = 2N_e \beta V_{A,0}$.

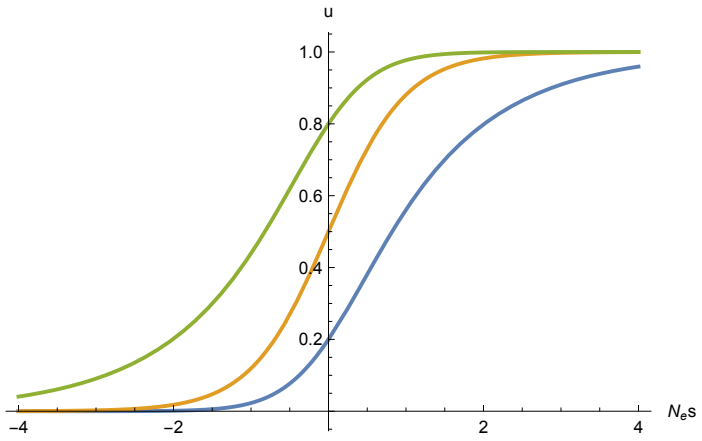
That is, the total change in mean due to selection is $2N$ times the change in the first generation.

Robertson (1960) derived this result in an ingenious way. We start with alleles that have effect α_i and initial frequency $p_{i,0}$. Ultimately, these alleles must be either lost or fixed, and so that $\mathbb{E}_\infty[\Delta \bar{z}] = 2\sum_i \alpha_i(u_i - p_{i,0})$, where u_i is its chance of fixation. There is a simple formula for u_i :

$$u_i = \frac{1 - e^{-4 N_e s_i p_{i,0}}}{1 - e^{-4 N_e s_i}} \quad \text{where } s_i = \beta\alpha_i \tag{1}$$

This shows u for $p_0 = 0.2,\ 0.5,\ 0.8$.

Out[ ]=



For weak selection ($Ns << 1$), $u_i - p_{i,0} \sim 2N_e s p_{i,0} q_{i,o} = 2N_e \beta \alpha_i p_{i,0} q_{i,o}$. Therefore,

$$R_\infty = 2\sum_i \alpha_i(u_i - p_{i,0}) \sim 4N_e\beta \sum_i \alpha_i^2 p_{i,0} q_{i,0} = 2N_e \beta V_{A,0} \tag{2}$$

which agrees with the simple quantitative genetic derivation. The underlying assumption is that selection is weak enough not to reduce genetic variance below the simple prediction $V_{A,0}\left(1 - \frac{1}{2N_e}\right)^t$, and that the change in mean is the cumulative effect of slight perturbations at very many loci.

The infinitesimal model predicts R_{50}well (Weber & Diggins, *Genetics*, 1990)

Extension to epistasis: Paixao & B (PNAS, 2016)

Robertson's argument extends to include dominance and epistasis. First, consider haploids. The additive variance decays with $(1 - F_t)$, but initial non-additive variance contributes to additive variance as $(1 - F_t)\, k F_t^{k-1}\, V_{A(k),t}$:

$$\mathbb{E}[V_{A,t}] = (1 - F_t)\,(V_{A,0} + 2\,F_t\,V_{AA,0} + 3\,F_t\,V_{AA,0} + \ldots) = (1 - F_t)\sum_{k=1}^{\infty} k F_t^{k-1}\, V_{A(k),0} \tag{3}$$

Summing over generations, with $1 - F_t = (1 - 1/N_e)^t$:

$$\mathbb{E}[R_\infty] = \beta\sum_{t=0}^{\infty}\mathbb{E}[V_{A,t}] = \beta\sum_{t=0}^{\infty}(1 - F_t)\sum_{k=1}^{\infty} k F_t^{k-1}\, V_{A(k),0} = \beta N_e \sum_{k=1}^{\infty} V_{A(k),0} = \beta N_e\, V_{G,0} \tag{4}$$

To the extent that $V_{G,0} > V_{A,0}$, epistasis increases the ultimate response - but this effect is limited.

In diploids, the effect of epistasis is stronger:

$$\mathbb{E}[R_\infty] = \beta N_e \sum_{k=1}^{\infty} 2^{k-1}\, V_{A(k),0} > \beta N_e\, V_{G,0} \tag{5}$$

However, because the k'th order component is ~ $(pq)^k$, and $pq \le \frac{1}{4}$, higher-order epistasis is still likely to make a small contribution to the ultimate response.

It is quite unclear how Robertson's (1960) argument from fixation probability would extend to include epistasis.

Limits with strong selection ($N_e s >> 1$)

What happens when selection is so strong that the infinitesimal model no longer holds - i.e. $N_e s$ large ?

We can predict the outcome by supposing that as alleles pass from low to high frequency (0.1 to 0.9, say), epistasis causes previously deleterious alleles to be favoured, and increase. Random pairwise epistasis can then increase the response (relative to the additive model), but not by much.

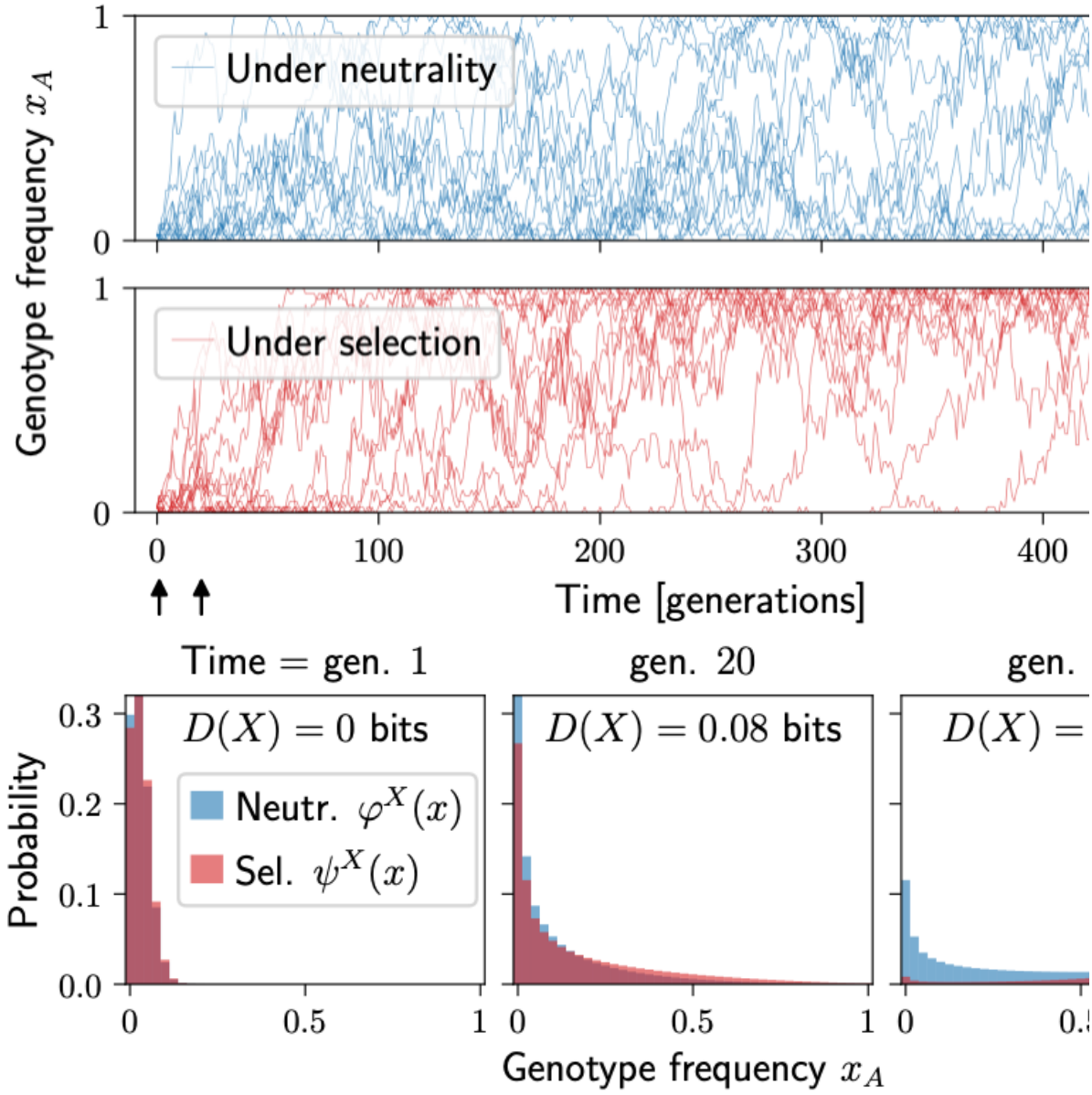
The figure shows simulations for n=50 loci (squares) or 1000 loci (circles); the additive model is in grey, and a model of pairwise epistasis in black $\left(\sigma_{a_i} = 0.1,\ \sigma_{\epsilon_{i,j}} = 0.5\right)$. The dashed line at left is the prediction from the infinitesimal model, and on the right, from the strong selection limit. From Paixao and Barton (*PNAS* 2016)

Accumulation of information (Hledik et al., *PNAS* 2023)

Natural selection concentrates populations around fit genotypes, and in this sense accumulates information (Kimura, 1961; Hledik et al., 2022):

$$D = \mathbb{E}\left[\log\left[\frac{\psi}{\psi_{\text{neutral}}}\right]\right] \tag{6}$$

For example, weak selection ($N_e s = 2$) biases allele frequencies towards the fitter allele:



There is a general bound on the rate of accumulation of information:

$$\triangle D \leq \frac{2}{\log[2]} N \operatorname{var}\left[\frac{W}{\overline{W}}\right] \tag{7}$$

At least for this simple example, selection is most efficient when alleles have *infinitesimal* effects.

Measuring the additive variance in fitness

If adaptation is due to weakly selected alleles ($N_e s \sim 1$), how can we detect it ?
Robertson (1961) argued that heritable variance in fitness would inflate the rate of random drift.
Santiago and Caballero (1995) showed that the rate of increase in allele frequency variance is:

$$\frac{pq}{2N}\left(\frac{1}{2} + \frac{\operatorname{var}[W]}{4} + \frac{V_a}{2c^2}\right) \tag{8}$$

where var(W) is the non-heritable variance in individual fitness, and V_a is the additive genetic

variance in individual fitness.

Buffalo and Coop (2020) analyse data from Barghi et al. (2019), showing how cov(Δp_t, $\Delta p_{t+\tau}$) decreases over time (A), and thereby estimating the fraction of variance in allele frequency change due to linked selection.

Exercises

1. Suppose that mutation increases the additive genetic variance by $V_m = 0.001\, V_E$ per generation.

i) What heritability would be maintained at equilibrium, in a population of $N_e = 1000$ diploid individuals, assuming no selection?

ii) Is it plausible that heritability is maintained by a balance between mutation and random drift?

iii) If instead, heritability is maintained by a balance between selection and mutation, roughly what selection coefficient must act on the underlying alleles?

iv) Suppose that we select on a population that is initially completely inbred; we select the top 35% of individuals, so that with a normal distribution, the selection differential is 0.5 phenotypic standard deviations. How much does the population mean change after 50 generations (i.e., what is the response to selection?)

2. In Weber and Diggins' (1990) experiment, the 20% of mated females with the highest ethanol resistance were selected to found the next generation.

i) Assuming that the trait is normally distributed, what is the mean of the selected females, in standard deviations ?

ii) If the initial heritability of ethanol resistance was 50%, what would be the predicted change in mean resistance after 65 generations, in a very large population?

iii) By how much would this be reduced in a smaller population, with effective size $N_e = 50$ individuals ?

iv) If a mutation arose, which increased ethanol resistance by 0.05 standard deviations, what would its ultimate probability of fixation be? What is its expected contribution to the response? What determines the relative contribution of large vs small effect mutations?

Note: Weber and Diggins (1990) give detailed explanations of their experimental design, and its effect on genetic variation. Here, you can make simpler arguments, but give your assumptions.

Stabilising selection

Observations

Organisms are described by an enormous number of traits, which typically follow a normal distribution. These traits together determine fitness, and a substantial fraction of their variance is genetic - as witnessed by resemblance between relatives, and rapid response to artificial selection. Direct evidence for stabilising selection is sparse: traits typically show strong associations with fitness, but this may not be stabilising, selection may not act via the measured trait, and there is publication bias (Kingsolver et al., 2001). Yet, since organisms retain the same form over long times, traits must be under stabilising selection, keeping them close to some optimum. This raises a paradox: if stabilising selection reduces variance, how is heritability maintained?

It is widely held that genetic variance is maintained by a balance between mutation and stabilising selection. This has the attraction that it is a universal explanation that involves (more or less) measurable parameters. However, even the equilibrium depends on genetic details which are hard to measure: specifically, on the distribution of effects of alleles on multiple traits and on fitness. The equilibrium theory is reasonably well understood, but how it relates to reality remains obscure.

This is surprising, given that *infinitesimal model* gives a robust and accurate understanding of the short term changes in trait means, and in that part of the variance due to linkage disequilibrium. However, the *genic* variance (i.e., the component due to diversity within loci) remains essentially unpredictable.

What do we know, and how do we know it?

$\boldsymbol{V_A/V_e}$: Genetic variance is largely additive, and typically is a substantial fraction of phenotypic variance: in other words, narrow sense heritability is high. Morphological traits tend to have high heritability (eg height in humans, >70%), whilst fitness components have lower heritability (25%, say) (Mousseau & Roff, 1987); these low values reflect higher environmental variance, not lower genetic variance (Houle, 2002).

$\boldsymbol{V_s}$: The prevalence of stabilising selection is mainly attested by the long-term stability of traits that can hardly be neutral. Direct measurements are made by quadratic regression of fitness

components on traits, and typically give large values (Kingsolver et al., 2001). However, these values often indicate *disruptive* selection. Moreover, it is impossible for strong stabilising selection to act on more than a limited number of traits. Most likely, there is strong stabilising selection on a limited number of traits, and weaker stabilising selection on very many more. In the theoretical literature, tracing back to Lande, there is a tradition of setting $V_s = 20\,V_e$, implying a load due to genetic variance of ~1/40 if $V_g = V_e$. However, this is arbitrary.

Replicability: In artificial selection experiments, it is striking that (at least, in reasonably large populations) response is highly replicable - implying a large # of genes (Barton & Keightley, 2002). Also, there is often no return of the mean towards the original value (e.g. Weber, 1996), as one might expect if the causal alleles had deleterious side-effects.

$\boldsymbol{V_m}$: The rate of increase of additive variance can be measured relatively easily, either by asking how quickly genetic variance increases, or measuring selection response, starting with a homogeneous population. Remarkably, this is $\sim 10^{-3}$ to $10^{-2}\,V_e$ for a range of traits and organisms (Halligan & Keightley, 2009; also reviewed in Lynch & Walsh, 1998).

$\boldsymbol{U = 2\sum\mu}$: The total deleterious mutation rate per diploid genome is very well known now, from direct sequencing of parents & offspring - ~60 for humans, say. The fraction of this that affects fitness (almost all for the worse) is fairly well known, by counting the fraction of sequence that evolves more slowly than the neutral baseline: ~2 for humans, say. The total rate of mutations affecting traits that affect fitness must be less than this, depending on pleiotropy. Some estimates can be found in Turelli (1984), but these are unreliable.

DFE: Many studies have estimated the distribution of effects of deleterious mutations, based on the distribution of allele frequencies at synonymous vs non-synonymous sites. Charlesworth (2015) reviews these, and compares them with quantitative genetic estimates of fitness variance; he concludes that there is a broad range, but $N_e\,s >> 1$ typically. Separately, there are estimates of the fraction of amino-acid substitutions that are adaptive, based on the McDonald-Kreitman (1991) test; see e.g. Keightley et al., 2016). There are more ambitious studies (e.g. Elyashiv et al., 2016) that make joint estimates of both deleterious mutations and positive selective sweeps; it is not clear whether such studies will converge on reliable estimates. Finally, Buffalo & Coop (2019) estimate the heritable variance in fitness from correlations in allele frequency change, based on an idea from Robertson (1961). To what extent is the net selection estimated here mediated via "traits" under stabilising selection?

$\boldsymbol{U\bar{s}}$: The rate of decline of fitness due to deleterious mutation has been measured in Drosophila by Shabalina et al. (1997) in a "middle class neighbourhood" experiment, as ~ 0.2 to 2% under benign and harsh conditions, respectively.

$\boldsymbol{n}$: The number of traits that are kept near their optimum by stabilising selection is presumably very large, but it is hard to know how even to define this number.

How all these observations together constrain the models is discussed in a series of reviews, from Turelli (1984), through Johnson & Barton (2005) to Walsh and Lynch (2018, Ch. 28).

Stabilising selection alone

Throughout, we will ignore the non-genetic "environmental" variance, V_e; we can imagine that we directly observe the genetic value, which indeed is possible in principle if we can produce large numbers of identical genotypes.

The infinitesimal model: reduction in V_g due to LD

In the classic model, suppose that initially there is a Gaussian distribution in the population as a whole, with variance V_g. With random mating, the variance in mid-parental values is $V_g/2$, and so after this is replenished by recombination, $V_g^* = \frac{V_g}{2} + V_0$. Thus, the population rapidly equilibrates at $V_g = 2\,V_0$.

Remarkably, Galton (1877) calculated the equilibrium between the reduction in variance due to stabilising selection, and its replenishment by recombination. Suppose we have V_g amongst offspring, before selection. Assume that fitness has a Gaussian form, $W[z] = \exp\left[-(z - z_{\text{opt}})^2/(2\,V_s)\right]$, where $1/V_s$ is a measure of the strength of selection. The distribution after selection is a product of two Gaussians: $\psi^*[z] = \psi[z] \times W[z]/\overline{W}$. This has variance $V_g^* = V_s\,V_g/(V_s + V_g)$. Therefore, at equilibrium, V_g before selection is given by:

$$V_g = \frac{V_s\,V_g}{2\,(V_s + V_g)} + V_0 \quad \text{hence } V_g \approx 2\,V_0\left(1 - 2\,\frac{V_0}{V_s} + O\left[\left(\frac{V_0}{V_s}\right)^2\right]\right) \tag{9}$$

In terms of the underlying genes, the difference between V_g and $2\,V_0$ is due to *linkage disequilibria*, which dissipate by 1/2 per generation. The constant component $2\,V_0$ is the *genic variance*, and is the sum of contributions from heterozygosity at individual loci; this remains constant under the infinitesimal model.

This model does not predict the genic variance: as we shall see, that evolves slowly, in a way that depends on the underlying genetic details.

Continuum of alleles: reduction in V_g due to selection

Now, consider the distribution of effects of a single locus. Although we are used to the simple-minded population genetic tradition of assuming two alleles, in general, there will be a continuous distribution of effects. This may be the typical case, if diverse regulatory sequences determine gene expression (say).

We can describe the distribution as $\psi[z]$; provided that alleles segregate independently (i.e., there is *linkage equilibrium*), the effect of stabilising selection on the distribution of effects of a single gene is the same as on the phenotype: $\psi^*[z] = \psi[z] \times W[z]/\overline{W}$. Assuming weak selection, and setting the mean and the optimum to zero, $W \sim 1 - z^2/(2\,V_s)$. Then, the new variance will be:

$$v^* = \frac{1}{\bar{W}} \int \left(1 - \frac{z^2}{2 V_s}\right) z^2 \psi[z] \, dz = \frac{1}{\bar{W}} \left(v - \frac{M_4}{2 V_s}\right)$$
$$\bar{W} = 1 - \frac{v}{2 V_s} \text{ for } v << V_s \text{ and so } v^* \approx \left(v - \frac{(M_4 - v^2)}{2 V_s}\right) \tag{10}$$

where M_4 is the fourth moment of the distribution of allelic effects of a single gene.

If the distribution is Gaussian, $M_4 = 3\,v^2$, and so $v^* \sim v - v^2/V_s$ for $v << V_s$; this is consistent with the exact formula for the product of two Gaussians, $V_g^* = V_g/(1 + V_g/V_s)$, given above. Summing over loci, we find that stabilising selection reduces the total genic variance by:

$$V_g^* = V_g - \frac{2}{V_s} \sum_i v_i^2 = V_g - \frac{V_g^2}{2 n_{eff} V_s} \text{ where } V_g = 2 \sum_i v_i \text{ and } \frac{1}{n_{eff}} = \frac{\sum_i v_i^2}{(\sum_i v_i)^2} \tag{11}$$

However, if the distribution is leptokurtic, stabilising selection reduces the variance by much more than this. Below, we will see that this has important consequences.

Two alleles: reduction in V_g due to selection

In population genetics, it is traditional to assume two alleles per locus. Suppose that alleles have additive effects α_i in diploids, so that individual phenotype is:

$$z = \sum_i \alpha_i (X_i + X_i^*) \tag{12}$$

where the states of the two genes are labelled X_i, X_i^*, with values 0 or 1; subtracting 1 from their sum is an arbitrary choice, which ensures that z lies between 0 and $2 \sum_i \alpha_i$. We ignore the random non-genetic component, to keep the analysis simple: we imagine that we can directly observe the genetic component of phenotype.

The mean and variance (entirely additive and genetic) are:

$$\bar{z} = 2 \sum_i \alpha_i p_i \qquad V_g = 2 \sum_i \alpha_i^2 p_i q_i + 2 \sum_{i \neq j} \alpha_i \alpha_j D_{ij} \tag{13}$$

The formula for the variance includes a component due to linkage disequilibrium (LD); in the following, we ignore this, and only follow allele frequencies. This will be accurate if selection is weak relative to recombination.

The effect of selection on allele frequencies can be found using Wright's *selection gradient*, and using that the mean fitness is a function only of the mean and variance:

$$\log(\bar{W}) \sim -\frac{(\bar{z} - z_{opt})^2}{2 V_s} - \frac{V_g}{2 V_s}$$
$$\Delta p_i = \frac{p_i q_i}{2} \frac{\partial \log(\bar{W})}{\partial p_i} = \frac{p_i q_i}{2} \left(\frac{\partial \log(\bar{W})}{\partial \bar{z}} \frac{\partial \bar{z}}{\partial p_i} + \frac{\partial \log(\bar{W})}{\partial V_g} \frac{\partial V_g}{\partial p_i}\right) = \tag{14}$$
$$p_i q_i \left(-\frac{(\bar{z} - z_{opt})}{V_s} \alpha_i + \frac{\alpha_i^2}{2 V_s} (p_i - q_i)\right)$$

since $\partial_p(pq) = -(p - q)$. The selection coefficient has two components: the first, $(\bar{z} - z_{opt})\,\alpha_i / V_s$, due to directional selection, and the second, $\alpha_i^2 (p_i - q_i)/(2 V_s)$, due to stabilis-

ing selection, which is equivalent to selection against heterozygotes. If (as will typically be the case) loci are near fixation, then stabilising selection dominates when the deviation from the optimum, $\Delta = \bar{z} - z_{\text{opt}}$, is smaller than half the allelic effect, $\alpha_i/2$.

If the mean is at the optimum ($\Delta = 0$), this equation suggests that we can fix any genotype: if $\Delta = 0$, then selection acts solely to reduce variance, and the only stable equilibria are at $p_i = 0$ or 1. However,the value of the fixed genotype will in general deviate from the optimum, so the outcome is **not** obvious.

Equilibrium between stabilising selection on a single trait and mutation

The equilibrium between stabilising selection and mutation is sensitive to the distribution of allelic effects - which are hard to observe directly. Therefore, whether a mutation/stabilising selection balance explains observed heritability remains obscure.

Continuum of alleles: Gaussian models

Continuum-of-alleles models have hardly been studied in population genetics, since they are mathematically much more challenging. Kimura (1965) introduced the model, applying it to understand the balance between mutation and stabilising selection, and it was developed further by Lande (1976). It then became prominent in the argument over the genetic basis of trait variation, following Turelli (1984). There is a separate and more recent literature, which uses continuum of alleles models to understand asexual adaptation - both elimination of deleterious mutations, and establishment of beneficial mutations; Hallatschek, Brunet, Desai and Rouzine have contributed. Here, random fluctuations in the numbers of the fittest class are crucial; stochastic continuum-of-alleles models are challenging.

Kimura (1965) considered mutations that have small effects relative to the standing variation. In this case, a diffusion approximation can be used, which has a Gaussian solution. We can then use the result already derived at the phenotypic level, and simply add the input due to mutation :

$$\Delta v_g = v_m - \frac{v^2}{V_s} \quad \text{for } v << V_s \tag{15}$$

where v, v_m are the variances due to a *single* gene. At equilibrium, $v = \sqrt{v_m V_s}$. Assuming n loci with equal mutational variance, so that $V_m = 2 n v_m$, we find:

$$V_g = \sqrt{2 n V_m V_s} \tag{16}$$

If we set $V_s = 20 V_e$ (a traditional choice), and $V_m \sim 0.001 V_e$, we find that $n = 25$ loci are enough to maintain $V_g = V_e$.

Latter (1970) studied the model further, but Lande brought it to prominence. Lande (1976a) extended Kimura's model to multiple loci, by assuming a *multivariate* continuum of alleles; this showed that linkage does not alter the genetic variance, because although negative LD reduces the variance, this is compensated by a relaxation of selection that allows an increase in genic variance. He applied the Gaussian model to study varied problems, including sexual selection, clines, speciation, and pleiotropy (1980, 1981, 1982).

Two alleles

Latter (1960) and Bulmer (1972) added mutation to Wright's (1935) model, and derived the equilibrium, assuming that the mean matches the optimum. Barton (1986) showed that there are typically very many alternative "adaptive peaks", corresponding to near-fixation of different genotypes. These genotypes may deviate substantially from the optimum , but allele frequencies adjust, bringing the mean closer to the optimum. Nevertheless, these "suboptimal" equilibria may have substantially inflated variance, which increases the load. Barton (1989) included the effect of drift, finding the rates at which populations move between peaks. This can be seen as a model of Wright's (1932) "shifting balance" theory of adaptation, which motivates both his analysis of stabilising selection and of allele frequency distributions (see the review and quantitative model in Coyne et al., 1997).

Barton (1986, 1989) assumed equal effects of loci, which is misleading: when effects are drawn from a distribution, there are still many equilibria, but they have more similar properties, and deviate less from the optimum (Vladar and Barton, 2014). Nevertheless, populations under the same selection will diverge, and eventually can become strongly reproductively isolated. However, this process has not been analysed for unequal allelic effects.

With two alleles, the equilibrium can easily be found:

$$\Delta p_i = p_i\, q_i \left(-\frac{(\overline{z} - z_{opt})}{V_s}\, \alpha_i + \frac{\alpha_i^2}{2\, V_s}\, (p_i - q_i) \right) + \mu_i\, (q_i - p_i) \tag{17}$$

If the mean is at the optimum, we find two equilibria:

$$p_i\, q_i = \frac{2\, \mu_i V_s}{\alpha_i^2} \quad \text{if } \alpha_i^2 > 8\, \mu V_s$$
$$p_i = \frac{1}{2} \quad \text{if } \alpha_i^2 < 8\, \mu_i V_s \tag{18}$$

Therefore, the genetic variance is:

$$V_g = 2 \sum_i \alpha_i^2\, p_i\, q_i \;=\; 2\, U^*\, V_s + \frac{1}{2} \sum_i \mu_i\, \alpha_i^2 \;<\; 2\, U\, V_s \tag{19}$$

Here, U^* is the total mutation rate to alleles with effects larger than the threshold, $\alpha_i > \sqrt{8\, \mu V_s}$; the additional term is due to alleles of smaller effect, whose frequency is dominated by mutation. One can easily extend this to include drift, using Wright's formula: then, the genetic variance is reduced, and converges to $2\, N_e\, V_m$ as drift dominates over selection.

This formula is remarkably simple, and independent of the allelic effects (above some threshold): large effect alleles are rarer, and so make the same contribution to the variance as small effect alleles. This is a manifestation of the mutation load, which is here a loss of fitness $V_g / (2\, V_s) = U$.

Continuum of alleles: the "House of Cards

We have qualitatively different predictions from the Gaussian continuum of alleles approximation, and the two-allele models. Turelli (1984) showed that the differences are not due to the number

of alleles, but rather, to the distribution of mutational effects. He developed the "House of Cards" approximation (introduced by Kingman, 1978) to show that if mutations have large effects (relative to the per-locus standing variation), then a continuum-of-alleles model gives the same predictions as Latter's (1960) two allele model.

Let the distribution of effects at a single locus be $\psi[z]$. We can imagine all kinds of mutation models. New mutations might add a random value to the current state; if this has small variance, we have Kimura's (1965) diffusion approximation, with a Gaussian solution. Alternatively, new mutations might have a value independent of the current state, with distribution Φ; the new mutation knocks down the existing "House of Cards" . If the distribution of mutational effects is has high variance, relative to the current distribution, then the "House of Cards" is a good approximation to the stepwise model.

Assuming the optimum is at $z = 0$, the equilibrium is given by:

$$\psi[z] = (1-\mu)\,\frac{W[z]}{\bar{W}}\,\psi[z] + \mu\,\Phi[z] = (1-\mu)\,\frac{1 - z^2/(2V_s)}{1 - v/(2V_s)}\,\psi[z] + \mu\,\Phi[z] \tag{20}$$

Hence, if $z^2 << V_s$:

$$\psi[z] = \frac{\mu\,\Phi[z]}{\left(\mu + \frac{1}{2V_s}\left(z^2 - v\right)\right)} \tag{21}$$

Necessarily, $v < 2\mu V_s$. Now, we must have $\int \psi dz = 1$, so we seek the solution:

$$1 = \int_{-\infty}^{\infty} \frac{\mu\,\Phi[z]}{\left(\mu + \frac{1}{2V_s}\left(z^2 - v\right)\right)}\,dz \tag{22}$$

Note that if this is satisfied, then necessarily, $v = \int_{-\infty}^{\infty} z^2\,\psi[z]\,dz$.

If we assume Φ is Gaussian, with variance σ^2, then

$$1 = \sqrt{\frac{\pi}{\beta - v/(2\sigma^2)}}\; e^{\beta - v/(2\sigma^2)}\;\beta\,\mathrm{Erfc}\left[\sqrt{\beta - v/(2\sigma^2)}\right] \tag{23}$$

where $\beta = \mu V_s/\sigma^2$. For $\beta << 1$ has the solution $v \sim 2\mu V_s$. Thus, if the variance of mutational effects, σ^2, is much larger than the standing variance, then we recover the HoC solution, $v \sim 2\mu V_s$.

Which regime?

The Gaussian continuum-of-alleles model can maintain variation more readily than when causal alleles are rare (i.e., in the House of Cards regime). However, this requires that the effect of mutations is small relative to the standing variation at a single locus (i.e., $\alpha^2 < v = \sqrt{v_m V_s}$). Since $v_m = \mu\alpha^2$, we have the condition that $\alpha^2 < \mu V_s$. Setting $\mu = 10^{-5}$, $V_s = 20\,V_e$, we have $\alpha < 0.014\,\sqrt{V_e}$. However, we also know that $V_m = 2n\mu\alpha^2 \sim 0.001\,V_e$, so $n > 3600$, which implies far too much genetic variance. A more direct way to see this problem is to see that if $V_g = \sqrt{2nV_m V_s}$, n~25 loci suffice for high heritability. However, $V_m = 2n\mu\alpha^2$, so with low per-locus mutation rates $(\mu = 10^{-5})$, α^2 has to be above the threshold magnitude to maintain the observed V_m. The Gaussian regime seems

feasible only if the responsible loci have exceptionally high mutation rates.

If we take the traditional $V_s = 20\,V_e$, then we require $U^* \sim 0.025$ to maintain $V_g \sim V_e$. The total rate of deleterious mutation is ~2 for mammals, estimated from the extent of regions that evolve more slowly than the neutral rate. GWAS show that very large numbers of SNP are associated with complex traits, and so this explanation seems feasible. However, there are clearly far more than ~100 "traits" which are kept near their optimum by stabilising selection, making it impossible that >100 separate sets of loci could each have $U^* \sim 0.025$. More plausibly, all functional regions of genome affect all traits: the "omnigenic" model (Boyle et al., 2017). Then, as we shall see in the following, the variance maintained for each of n traits is ~ $2\,U V_s/n$. It seems impossible for large numbers of traits to be maintained by *strong* stabilising selection. Possibly, only a few traits are strongly selected, whilst the remainder are maintained by much weaker selection (i.e., large V_s). Perhaps then, there might be enough mutation to maintain heritability in large numbers of traits.

Anticipating the following section, note that the continuum of alleles model becomes highly implausible when one considers multiple traits: there must be enough alleles segregating to sustain a smooth *multivariate* distribution (Turelli, 1985, Barton, 1990)

Pleiotropy and multiple traits: mutation/selection balance

Joint distribution of $\{\alpha, s\}$

Mackay (1987) made random transposable element insertions into *D. melanogaster*, and measured their joint effect on viability and on bristle number (the classic trait in Drosophila). This suggested pleiotropic models, where mutations affect fitness and also the trait. Keightley and Hill developed such models, using Wright's stationary distribution to include selection, mutation and drift (Keightley & Hill, 1998; Zhang & Hill, 2005).

Consider the simplest case, where mutations have equal additive effects, changing the trait by $\pm\alpha$, and reducing fitness of heterozygotes by s. Allele frequency is μ/s, and so the genetic variance is:

$$V_g = \sum_i 2\,\alpha^2\,p_i\,q_i \;\approx\; \sum_i 2\,\frac{\mu_i}{s}\,\alpha^2 \;\approx\; \frac{V_m}{s} \tag{24}$$

There is simply a balance between the input of variance by mutation, V_m, and the elimination of mutations at rate s. If there is a distribution of α, s then the genetic variance is proportional to $\mathbb{E}[\alpha^2/s]$; if there are many alleles that affect the trait, but do not much affect fitness, then trait variance will be high. One can think of s in the above formula as a harmonic mean, weighted by α^2. This obviously breaks down as s→0: then, we must include drift.

Keightley and Hill (1998) assume a distribution of allele frequencies, and of $\{\alpha, s\}$. Using Wright's formula, assuming deleterious allele frequency $p << 1$, total mutation rate $U = 2\sum_i \mu$ and μ equal across loci:

$$V_g \approx \sum_i 2\,\alpha^2\,p_i\,q_i \;\approx\; U\,\mathbb{E}\left[\int_0^1 \left(2\,\alpha^2\,p\right)\,p^{4N\mu-1}\,e^{-4N_e sp}\,dp \Big/ \int_0^1 p^{4N\mu-1}\,e^{-4N_e sp}\,dp\right] \tag{25}$$

where the expectation is over the joint distribution of $\{\alpha, s\}$. For $N_e s >> 1$, this converges to V_m/s,

and for $N_e s$ small, to a mutation-drift balance, $2 N_e V_m$.

Suppose that we include the effect of stabilising selection, as well as the pleiotropic effect of the mutation. For rare alleles, the net selection is now $-s - \frac{\alpha^2}{2 V_s}$. Thus, in the simplest case of equal $\pm\alpha$, s:

$$V_g = \sum_i 2\,\alpha^2\,p_i\,q_i \approx \sum_i 2\,\frac{\mu_i}{\alpha^2/(2\,V_s)+s}\,\alpha^2 \tag{26}$$

If $s >> \alpha^2/(2\,V_s)$, then $V_g \sim V_m/s$, whereas if $s << \alpha^2/(2\,V_s)$, $V_g \sim 2\,UV_s$, as we saw before. Under this combined model, V_g must be smaller than either of these estimates. Note that we have good estimates that $V_m/V_g \sim 0.001 - 0.01$, implying that the net "effective" selection is 0.1% - 1%, regardless of the causes of that selection. (Assuming that we are in the rare allele/House of Cards regime).

Apparent stabilising selection

Even if the trait does not affect fitness, it may appear to: individuals carrying more deleterious mutations will tend have more extreme trait values, and so mean fitness will decline with deviations from the average (Barton, 1990; Kondrashov and Turelli, 1992). The strength of the apparent V_s is such that the *apparent* load due to stabilising selection is roughly $V_g/(2\,V_s) \sim s/2$, though this depends strongly on the distribution of $\{\alpha, s\}$. This implies that observations of strong stabilising selection on traits are unlikely to be due to this effect.

Multiple traits

Another way of modelling pleiotropy is to suppose that there are a very large number of traits, each under stabilising selection. At a mutation-selection balance, this is equivalent to assuming that the pleiotropic s in the above models is due to deviations from the optimum of a myriad of cryptic traits. However, the models are not completely equivalent: if mutations are unconditionally deleterious, they will accumulate unless $N_e s$ is large, and the population will collapse. In contrast, under the stabilising selection model, populations will wander around the optimum, but will reach a quasi-steady state in which mutations can compensate each other.

Using the simple model above, and assuming V_s is the same for all of the n traits (which we can make true by definition), we have:

$$V_{g,1} = \sum_i 2\,\frac{\mu_i}{\alpha_1^2/(2\,V_s)+\sum_{k=2}^{n}\alpha_k^2/(2\,V_s)}\,\alpha_1^2 = 2\,UV_s\left(\frac{\alpha_1^2}{\alpha_1^2+\sum_{k=2}^{n}\alpha_k^2}\right) \tag{27}$$

We see that the single trait HoC prediction $2\,UV_s$ is reduced by a factor $\sim n$, if mutations that affect the focal trait $k = 1$ also affect $n - 1$ other traits. If we imagine "universal pleiotropy", then U is the total rate of mutations that have any effect on fitness; with $U = 2$, $V_s = 20\,V_e$, we require $n \sim 80$ to allow high heritability. To see this another way, the total load, summing $V_g/(2\,V_s)$ over all traits, is necessarily U. Therefore, there cannot be very many strongly selected traits.

An intriguing consequence of pleiotropic models is that increasing stabilising selection on one trait reduces the frequency of all alleles that affect that trait, and therefore, reduces genetic

variance overall. Therefore, we do not expect to see a close relation between the strength of stabilising selection and the corresponding genetic variance. It is not clear how strong this relation is empirically, or how far epistatic modifiers can shape the genetic variance (see recent work by Houle).

Predictions from Fisher's Geometric model: Simons et al. (2018)

Simons et al. (2018) analyse stabilising selection on very many traits (a.k.a. Fisher's Geometric Model). They find that in the limit of large n, there is a robust joint distribution of allele frequencies and effects, which can be tested against GWAS data; they estimate $s \sim 0.001$, consistent with the simple V_m / V_g argument. The key assumption here is that mutations have a vector of effects, with magnitude drawn from some distribution, and random direction.

This issue is closely related to the question of how a high mutation load ($U \sim 2$) can be sustained. Kimura and Maruyama (1966) showed that with sexual reproduction *and* negative epistasis, deleterious mutations can be eliminated more efficiently, so that mean fitness can be much higher than e^{-U}; Kondrashov (1988) developed this as an argument for how sexual reproduction can be maintained, despite its costs. If we imagine deleterious effects as being due to deviations from an optimum, then we require that the log fitness declines more steeply than quadratically with distance from the optimum. There has been a good deal of empirical work, trying to detect negative epistasis, but results are equivocal. It is not clear how this would affect the amount of variance maintained, or why this special kind of epistasis should have evolved. Again, an interesting open question...

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