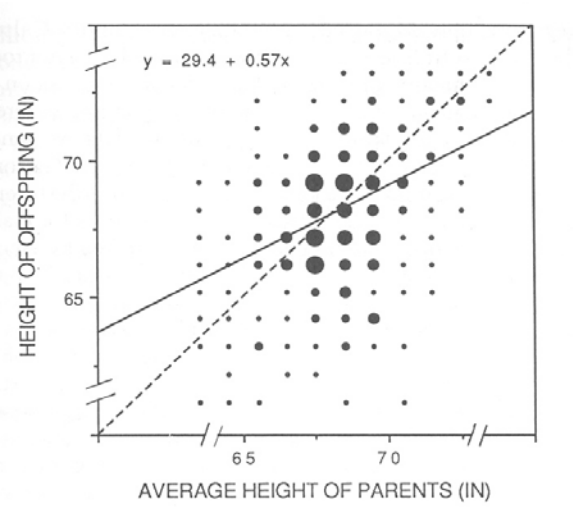
Chapter 5: Inheritance of a Single Trait

Overview.- When a trait is affected by many genes, a statistical concept of inheritance can be used to predict how the effects of selection will be transmitted to the next generation. This statistical concept (genetic variance) can also be used to model the effects of selection over evolutionary time. The standing crop of genetic variation in a population can be visualized as a balance between the opposing effects of selection and mutation. Genetic variation is nibbled away each generation by selection, but variation is restored by mutation and other processes (recombination and migration). Studies of the mutation process reveal an appreciable per generation input to many traits. Because selection is often weak, mutation in conjunction with recombination and migration can compensate for selective losses. Consequently, the standing crop of genetic variation is substantial in most populations for many kinds of traits. The standardized genetic variance (heritability) of traits is typically in the range 0.2-0.6 (on a scale that ranges from 0-1).

5.1 Phenotypic resemblance between parents and offspring reveals heritable variation

Before the rediscovery of Mendelism, Francis Galton (1898) quantified inheritance with parent-offspring plots. Galton focused on a variety of human traits, but especially on easily measured attributes such as stature. Compiling records on 554 (ck) families, Galton plotted the average height of both parents (mid-parent) as a function of the average height of offspring in a family (mid-offspring). His data are shown in Figure 5.1 {from Arnold 1994}, which follows the contemporary convention of plotting offspring as a function of parents. Noting that the least-squares fit of such data always have a lesser slope than perfect inheritance, Galton referred to the fitted line as a 'regression'. Focusing on the regression line, we see that the offspring of tall parents regress towards the average, and so do the offspring of short parents. The slope of Galton's regression line was later known as heritability. As we shall see, heritability is of key importance in summarizing the inheritance of a trait affected by many genes and in transmitting the effects of selection from one generation to the next.



5.2 A model for phenotypic value

The statistical underpinnings for Galton's observation of parent-offspring resemblance were independently discovered by Weinberg (1909), Fisher (1918), and Wright (1921). Working in the period following the rediscovery of Mendelism and independently because of WW I, Weinberg, Fisher and Wright took the same perspective on the kinds of continuously-distributed traits studied and plotted by Galton. The new perspective was to ask whether Galton's regression was a natural consequence of multiple factor (polygenic) inheritance.

We now turn to a particular version of that polygenic model for inheritance with the aim of understanding the Mendelian basis for Galton's regression slope, which we shall call h^2. For the moment we will ignore dominance and epistasis. Putting those genetic complications aside, the model takes a simple form. Let us assume for simplicity that the effects of alleles at those many polygenic loci are added together to constitute an individual's *genetic* or *breeding value*, x. We shall consider the genetic values of all individuals in a population to be a random variable with standard statistical properties (e.g., x

has a distribution that can be characterized by a mean, variance, etc). We will also assume that the trait in question is affected by a host of environmental factors. We will call the sum of all those environmental factors, *e*, the individual's *environmental value*. Turning to the population, we assume as before that *e* is a random variable that can be characterized in the standard way. Finally, let us assume that an individual's phenotypic value, *z*, is simply the sum of its genetic and environmental values,

$$z = x + e \,. \quad (5.0)$$

Although *x* and *e* are invisible to us, we can measure or count an individual's phenotypic value, *z*. This elementary fact, the observability of *z*, sets the stage for all that follows. Because *z* is a random variable that is the sum of two other random variables, *x* and *e*, we can infer the statistical properties of *x* and *e* from those of *z*. To proceed we shall make one more key assumption, that *x* and *e* are independent (uncorrelated) variables. From these assumptions we can show that the means and variances of our three random variables are related in a simple, additive way,

$$\bar{z} = \bar{x} + \bar{e} \,, \quad (5.1)$$

$$P = G + E \,. \quad (5.2)$$

The three variances are phenotypic (*P*), genetic (*G*), and environmental (*E*). So far we have made no assumptions about the distributions of *z*, *x* and *e*. It is natural to assume, however, that *x* and *e* are normally distributed, because we know from the Central Limit Theorem that the sum of many random variables is normally distributed, no matter what the distributions of those many random variables may be (Fig. 5.2). Consequently, *z* will be normally distributed as well.

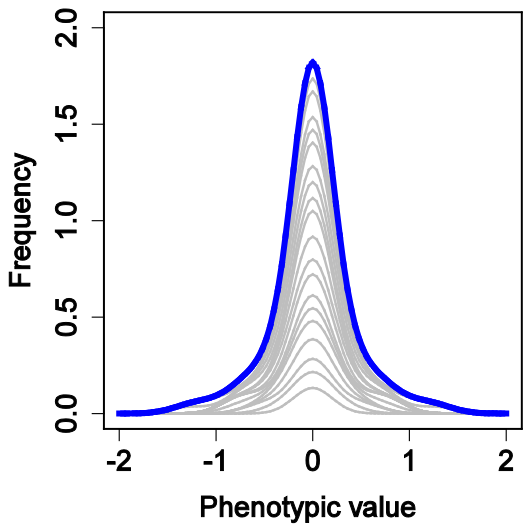


Fig. 5.2 The distribution of phenotypic values as the sum of underlying genotypic distributions, showing that the sum rapidly converges on a normal distribution. In this example, each of 20 genes contributes a slightly to moderately trimodal distribution in which the value of the heterozygote is 0 and the values of the two homozygotes are symmetrical about zero with an absolute value drawn from a normal distribution (mean = 0, standard deviation = 0.75). The environmental variances of the three genotypes at a locus are each 0.04, and the three genotypes occur at a 1:2:1 ratio. The gray curves show the accumulated frequency distributions of 1, 2, 3 … 19 loci. The blue curve shows the accumulated distribution when the trimodal contributions of 20 loci are summed.

We are now in a position to understand Galton's regression slope. For simplicity, consider first the covariance between the phenotypic values of one parent and mid-offspring. If we substitute $x + e$ for both kinds of phenotypic values into our standard expression for a covariance (1.5), we produce four covariance terms, but all but one are zero. The one term that remains is one half the covariance between the breeding values of parents and offspring which is equivalent to half the genetic variance. The algebra

is only slightly more complicated if we use mid-parent values instead of single parent values, and we obtain

$$h^2 = Cov(z_o, z_p)P^{-1} = Cov(x_o, x_p)P^{-1} = GP^{-1} = G/P, \quad (5.3)$$

where h^2 is the *heritability* of the trait, and the *o* and *p* subscripts denote mid-offspring and mid-parents, respectively. In other words, the regression of mid-offspring on mid-parental phenotypes estimates G/P, which we call the heritability of the trait, h^2 (Fig. 5.3 = theoretical parent-offspring regressions). From (5.2 and 5.3), we can see that h^2 varies from zero to one. From Galton's plot we can estimate the heritability of human stature as 0.57.

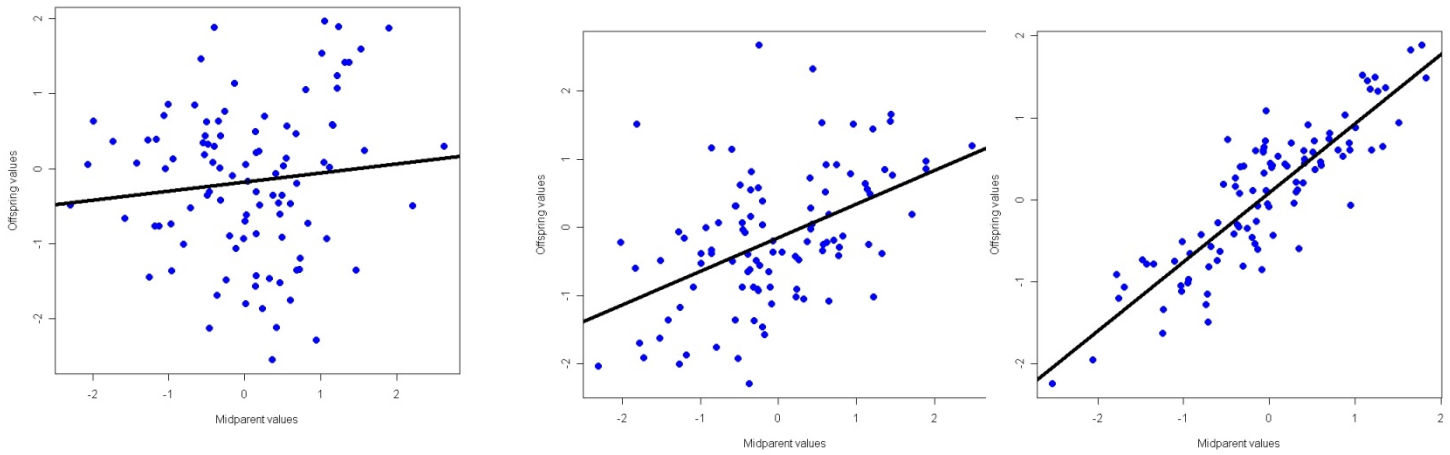


Figure 5.3. Hypothetical examples of offspring vs. midparent value plots. Each plot portrays a sample of 100 offspring-parent values from a bivariate normal distribution.(a) In the parametric distribution, h^2=0. In the sample, h^2=0.12 ± 0.11 s.e. (b) In the parametric distribution, h^2=0.5. In the sample, h^2=0.49 ± 0.09 s.e. (c) In the parametric distribution, h^2=0.8. In the sample, h^2=0.84 ± 0.05 s.e. *Put parametric values for h2 on plot*

5.3 A general expression for the covariance among relatives

To obtain a general expression for covariance among relatives, we start with a more general model. This more general model includes the effects of dominance and epistasis, as well as additive genetic effects. In a later section, we will discuss how each of these effects represents contributions from many loci, as well as from the different alleles at a locus. For now we are concerned only with how these three three kinds of aggregate effects contribute to phenotypic value and resemblance among relatives. In a model for phenotypic value that includes genetic parts arising from dominance, *y*, and epistasis, *i*,

$$z = x + y + i + e. \quad (5.4)$$

Dominance refers interaction between the alleles at the same locus so that interactions are nonadditive. For, example, if one allele is dominant, the other allele has no effect on phenotypic value. In similar way, epistasis also denotes interaction, but now the interactions are between alleles at different loci. Not surprisingly, the term for epistasis in includes many kinds of possible interactions,

$$i = i_{AA} + i_{AD} + i_{DD} + i_{AAA} + i_{AAD} + i_{ADD} + i_{DDD} + \ldots \text{ , (5.5)}$$

in which *AA* denotes interactions between additive effects taken two at a time, *AAA* denotes three-way interactions between additive effects at three different loci, etc. Mixed subscripts (e.g., *AD*, *AAD*) denote interactions between the additive and dominance effects of different loci. This more complicated model for phenotypic value can be substituted into the formula for covariance (1.5). Algebraic manipulation leads to a general expression for the composition of phenotypic covariance than includes dominance and epistatic effects. In other words, this general theoretical result partitions phenotypic covariance between particular kinds of relatives (*X* and *Y*) (e.g., *X* =parents and *Y*= offspring, or *X*= uncles and *Y*= nephews) into genetic parts (variances) attributable to additive effects (*A*), dominance (*D*) and epistasis (e.g., *AA*, *ADD*):

$$Cov(X,Y) = rG + uG_D + r^2G_{AA} + ruG_{AD} + u^2G_{DD} + r^3G_{AAA} + r^2uG_{AAD} + ru^2G_{ADD} + u^3G_{DDD} + \ldots \quad (5.6)$$

(Cockerham 1959). In this expression, *r* is the *coefficient of relationship* (the probability that relatives *X* and *Y* have the same allele through *identity by descent*), and *u* is *coefficient of consanguinity* (the probability that two alleles at a locus drawn at random, one each from *X* and *Y*, will be identical by descent). The first coefficient describes the inheritance on a single allele and hence additive effects, while the second describes the inheritance of pairs of alleles and hence dominance deviations (Crow and Kimura 1970, Falconer and Mackay 1996). For example, *rG*, the product of *r* and additive genetic variance, uG_D is the product of *u* and dominance variance, r^2G_{AA} is the product of r^2 and the covariance of additive effects at pairs of loci, etc. The two coefficients, *r* and *u*, can be determined for various kinds of relatives (e.g., full sibs) from a pedigree are presented in Table 5.1.

Table 5.1. Coefficients of relationship (r), consanguinity (u), and the contribution of maternal effects for various kinds of relatives (from Willham 1963). An asterick (*) denotes a relatively minor contribution of maternal effect.

Relatives	r	u	Maternal effect contribution
Mother-offspring	½	0	yes
Father-offspring	½	0	no*
Full-sib	½	¼	yes
Paternal half-sib	¼	0	no
Maternal half-sib	¼	0	yes
Double first cousins (fathers full-sibs, mothers full-sibs)	¼	⅛	yes
Double first cousins (both opposite sexes are full-sibs)	¼	⅛	yes
Single first cousins (fathers full-sibs)	⅛	0	no
Single first cousins (mothers full-sibs)	⅛	0	yes

The importance of G to parent-offspring resemblance can be understood by realizing that for these relatives $u = 0$, and consequently expression (5.6) is greatly simplified and involves only G, G_{AA}, G_{AAA}, etc. In other words, dominance makes no contribution to the phenotypic resemblance between parents and offspring. The collective contribution of epistasis to parent-offspring resemblance is likely to be small for the following reason. The coefficient of relationship for parents and offspring is ½, consequently when is it raised to progressively higher powers as the coefficient for higher order terms describing additive-by-additive epistasis (*AA*, *AAA*, etc), the net effect is a progressive lowering of contributions. In other words, in practical terms we can ignore the contributions of epistasis and view resemblance between parents and offspring, as in Galton's plots, as providing a virtually clean estimate of additive genetic variance. In a similar way, paternal half sibs are useful for estimating G because $r = ¼$ and $u = 0$. In contrast, certain other relatives provide problematic estimates of G because dominance does contribute to phenotypic resemblance. Full sibs are a case in point. Because full sibs have two parents in common, $u = ¼$ and $r = ½$. Ignoring epistasis, we see from (5.6) that the resemblance among full sibs springs from two terms, $\frac{1}{2}G + \frac{1}{4}G_D$, not just from additive genetic variance as in the parent-offspring case. To make matters worse, full sibs also share a maternal environment and that sharing can also contribute to phenotypic resemblance.

In general, maternal effects can contribute to resemblance between mothers and their offspring and to other kinds of relatives. The kinds of relatives that are affected in the Willham (1963, 1972) model of maternal effects are shown in Table 5.1. In the Willham model, one kind of trait expressed in mothers affects the same trait expressed in offspring. For example, milk yield in a female mammal affects milk yield in her female offspring. The model allows the trait to be heritable (with dominance effects, as well as additive genetic and environmental parts), so multiple maternal pathways can contribute to mother-daugther resemblance in, say, milk yield. Table 5.1 tell us that if we wish to avoid the complications that this kind of maternal effect exerts on an estimate of additive genetic variance, then three kinds of relatives are particularly useful (father-offspring, paternal half-sibs, and single first cousins in which fathers rather than mothers are full-sibs). The Kirkpatrick-Lande (1989, 1992) model of maternal effects allows one trait in mothers to affect the expression of another or the same trait in offspring. This more general model make the same qualitative predictions about the usefulness of relatives as does Willham's model (Table 5.1)

Phenotypic resemblance arising from shared environments, maternal or otherwise, is a complication that must be considered in the estimation of additive genetic variance and similar genetic parameters. In terms of our model (5.6), the complication means that although we assumed that the covariance between the environments of two relatives was zero, when environments are shared that may not be a safe assumption. The genetic aspect of resemblance between relatives is rooted in Mendelism and so submits to a general treatment (5.6). In contrast, the environmental aspect of resemblance depends on the ecological peculiarities of individual species, making generalization difficult. A standard approach is to experimentally manipulate rearing environments so that contributions to phenotypic resemblance can be isolated and assessed. For example Smith & Dhondt (1980) used cross-fostering in to study phenotypic resemblance in a song bird on a small island that allowed access to all nests. By swapping eggs between nests, they were able to compare actual parent-offspring resemblance with foster parent-foster offspring resemblance (Fig. 5.4). In this case, the shared environment is the territory which is shelters and nutures successive generations. Apparently, however, the shared territory of foster parents and their foster offspring makes no contribution to phenotypic resemblance in body size. These and other kinds of experimental manipulations can be used to test for, and evaluate the magnitude of, the contribution of shared environments.

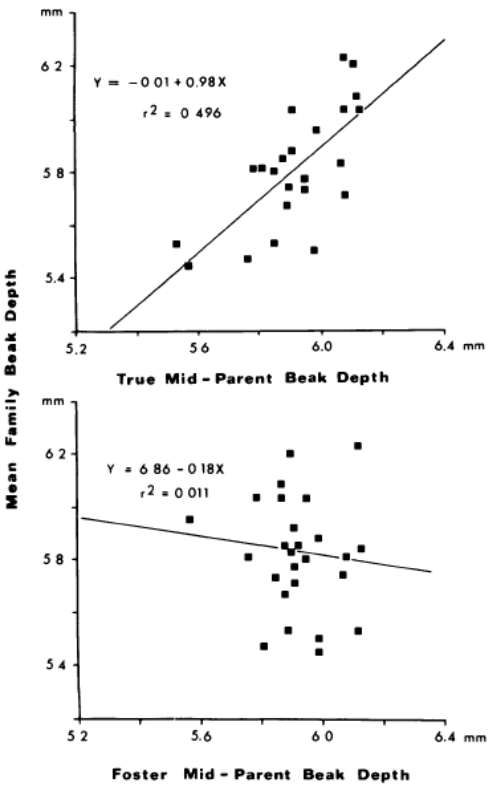


FIG. 1. Beak depths (mm) for true mid-parent (above) and foster mid-parent plotted against mean beak depth for families of young song sparrows captured from 40 broods interchanged as eggs or 1–3 day old nestlings.

5.35 Additive genetic and dominance effects at individual loci

In presenting a model for phenotypic values in section 5.3, we cavalierly used variables that represented the sum of effects over all loci in the genome. It will help to make those concepts more concrete, if we consider those same effects at the level of individual loci, before the summation takes place. The following account is based on Fisher's (1958) somewhat opaque exposition and Falconer & Mackay's (1996) portrayal of that exposition. For simplicity we will consider a locus, A, with just two alleles, A_1 and A_2. We define the genotypic values of each genotype as the average trait value of a large sample of individuals with that genotype. It is convenient to scale the trait values of the genotypes, so that trait value midway between the two homozygotes is zero. On this scale we will refer the the genotypic values of the genotype with the lowest score, say A_1A_1, as $-a$ and the value of the genotype with the highest score, say A_2A_2, as $+a$. We shall denote the genotypic value of the heterozygote, A_1A_2, as d. Thus, in the absence of dominance $d = 0$. These conventions for the contributions of a particular genotype to an individual's phenotypic value are straightforward, but a moment's reflection tells us that if we want to relate these genotypic values to average genetic value in the population, we will need to know the frequencies of the three genotypes. A simple way to proceed, is the let p denote the

frequency of the A_1 allele, so that the frequency of the A_2 allele is *q=1-p*, and assume Hardy-Weinberg proportions for the genotypes. Skipping over the details of the algebra, which are sketched in Falconer & Mackay (1996), we can show that the average effects on the trait mean of substituting one allele for another are

$$\alpha_1 = q[a + d(q - p)]$$

$$\alpha_2 = -p[a + d(q - p)],$$

where $\alpha_1$is the average effect of A_1 and α_2 is the average effect of A_2. Averaging the effects of these two kinds of substitutions across genotypes, we find that the average effect of a gene substitution at this locus is

$$\alpha = a + d(q - p) = \alpha_1 - \alpha_2.$$

The point of these definitions and this algebra is that we are now in a position to see the relationship between the genotypic value and breeding value, *x* (Table 5.2). The genotypic value of a genotype is a simple quantity that does not change with gene frequency. In contrast, the breeding value of a genotype does change with gene frequency, taking account of the fact that the consequence of substituting one allele for another will depend on the frequencies of the two alleles. The allelic property that incorporates this frequency dependence is average effect. The definitions of the average effects of alleles at a locus may seem awkward, but they allow us to achieve the simple result that the breeding value of a genotype is simply the sum of average effects of its alleles. Furthermore, the contribution of allelic variety at a locus to additive genetic variance is simply the variance in breeding values at that locus. These same relationships hold if we allow multiple alleles at a locus, and if we allow multiple loci to affect the trait. Effects are summed over all alleles at a locus and across all loci to yield the total breeding value of an individual and additive genetic variance is the variance of those multi-locus breeding values.

Table 5.2 The relationship between genotypic and breeding values at a single locus and the contribution of that locus to additive genetic variance for the trait.

Genotype	Frequency	Genotypic value	Breeding value, *x*
A_1A_1	p^2	$-a$	$2\alpha_1 = 2q\alpha$
A_1A_2	$2pq$	d	$\alpha_1 + \alpha_2 = (q - p)\alpha$
A_2A_2	q^2	$+a$	$2\alpha_2 = -2p\alpha$
mean		$a(p - q) + 2dpq$	0
variance			G

Part of the complexity in distinguishing between genotypic value and breeding value arises from dominance. In the absence of dominance, $d = 0$, and $a = \alpha$, but of course breeding values are still a function of gene frequency. Ignoring epistasis, the difference between genotypic value and breeding value is known as the *dominance deviation*, *y*, of that genotype. Like breeding value, *x*, dominance deviations, *y*, represent the sum of effects over loci. Dominance deviations are functions of gene frequency, unlike *d* which is simple property of a heterozygous genotype,

irrespective of gene frequency. Dominance variance, *D*, is in turn a function of variance in dominance deviations.

5.4 Estimating additive genetic variance using covariance of relatives

In the covariance approach, replicated sets of relatives (e.g., parents and offspring) are assembled either by direct sampling from nature or by conducting breeding designs. Additive genetic variance, *G*, can then be estimated with varying degrees of fidelity, depending on the kinds of relatives that are used and the sample size that is employed. Estimation of *G* is a statistical procedure conducted by regression or analysis of variance (ANOVA). In the next section we will give examples of the regression approach that is commonly used to analyze parent-offspring data. In the ANOVA approach, the focus is on estimating components of variances (e.g., the among-sire component of variance, covariance among paternal half-sibs) that bear a simple mathematical relationship to additive genetic variance. So, for example, four times the among sire component of variance gives an estimate of additive genetic variance. Falconer and MacKay (1989) and Lynch and Walsh (1998) provide details for analyzing several important breeding designs.

We want an interval as well a point estimate of *G*. In other words, we want to know how much confidence to place on the single value that we present as our estimate of *G*. In most implementations of the covariance approach, family size will vary, often appreciably. Unfortunately, analytical solutions for the standard error of G assume equal family sizes and solution do not exist for the unbalanced case. This is one problem that spurred the development of the animal model, which is reviewed in section 5.xx. Another solution is to imbed the ANOVA implementation in a resampling scheme such as bootstrapping that can provide standard errors (e.g., Phillips and Arnold 1999).

Garter snake vertebral numbers provide an example of *G* estimation using the covariance approach (Arnold & Phillips 1999, Phillips and Arnold 1999). A set of 151 mothers and their 712 female offspring was assembled by capturing pregnant females at a single locality in nature and holding them in the laboratory until their litters were born. The number of body and tail vertebrae can be conveniently assessed by counting scales on the ventral surface, with the transition between the two regions demarcated by a distinctive vent scale. The counts do not change during the postnatal life of the individual, except that the tips of the tail can sometimes be lost during predation attempts or skin-shedding. In that case, the conical scale at the tip is missing and the count can be scored as missing. Vertebral counts in fishes are known to be affected by temperature during development, but garter snake females assiduously thermoregulate during pregnancy, with only modest differences among females. Furthermore, holding females at different constant temperatures during pregnancy reveals flat reaction norms (offspring vertebral counts as a function of temperature)(Arnold and Peterson 2002). These and other considerations suggest that the two counts are not subject to maternal effects. Consequently, we can reasonably estimate additive genetic variance for vertebral counts by regressing average daughter counts on the counts of the mothers (Fig. 5.5). The resulting estimates of heritability for body and tail counts are 0.54 ±0.10 s.e. and 0.48 ± 0.10 s.e., respectively. Standard errors were estimated by bootstrapping.

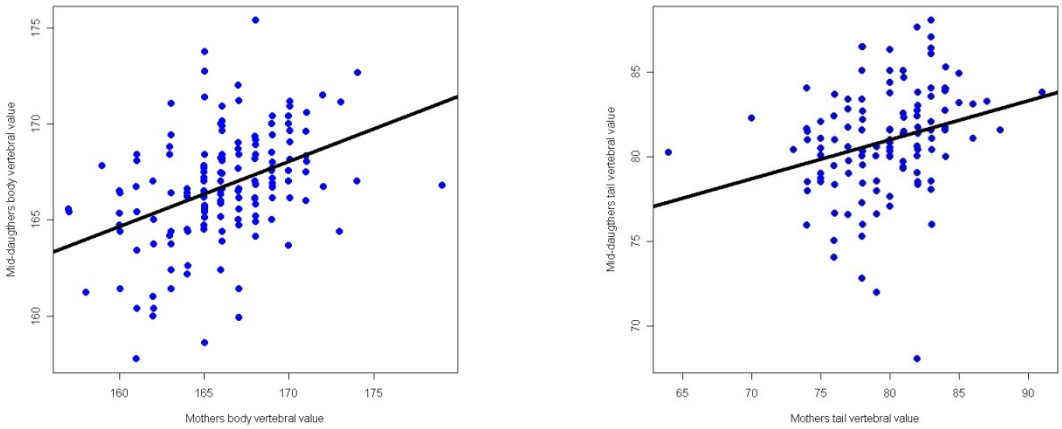


Figure 5.5 Offspring vs. parent heritability plots in the garter snake *Thamnophis elegans* (inland population). (a) The average body vertebral count of daughters is plotted against the mother's count: n = 151, corresponding to a estimated genetic variance of 8.17 ± 1.70 s.e., h^2 = 0.54 ±0.10 s.e. (b) The average tail vertebral count of daughters is plotted against the mother's count: n = 120, corresponding to an estimated genetic variance of 8.16 ± 1.73, h^2 = 0.48 ± 0.10 (Arnold & Phillips 1999).

5.43 The utility of pedigrees

One needs replicated sets of relatives to estimate genetic variance using the covariance approach. With many kinds of organisms such sets are difficult to assemble or many different kinds of relatives are available. In either of these situations it may be practical to estimate the pairwise relationships of individuals using genetic markers and assemble that information into a pedigree that straddles multiple generations. Having phenotypic scores for a large sample of individuals of known pedigree opens the door to *G* estimation, as well as studies of inbreeding depression and sociality (Pembertson 2008).

5.44 Estimating of genetic variance using pedigrees: introduction to the animal model

Pedigree analysis is a powerful alternative to using covariance among relatives to estimate genetic variance. The advantage of pedigree analysis is flexibility that allows it to simultaneously incorporate information from different kinds of relatives while accounting for a variety fixed or random effects, such as sexual dimorphism, maternal effects, region-specific environmental effects (Pemberton 2008, Thompson 2008). The analysis that accomplishes all of this is based on the animal model, which was pioneered especially by Henderson (1976, 1984). The animal model is a special case of a mixed model that includes both random and fixed effects. The animal model was inspired by the common situation in animal breeding that rearing often happens in different environments (herds) and in different times (years). Furthermore, family sizes are often different so that data are unbalanced, creating problems in attaching standard errors to variance components (Henderson 1984, Searle 1987 book). The following account of the animal model closely follows Henderson's (1984) description.

The animal model has two parts; one part that specifies the composition of the phenotypic values, z, of all the individuals in a sample and another part that specifies the distributions of the random variables that make up z. In a sample of n individuals, let the phenotypic values of the ith individual be

$$z_i = \mu_j + u_k + e_i \,,$$

where μ_j is a fixed effect, u_k is a random effect , and e_i is a residual effect, not accounted for by the fixed and random effects in the model. The expressions of all the individuals in the sample can be written in matrix form as

$$z = Xb + Zu + e,$$

where

b is a fixed, usually unknown column vector of length *p*, giving the contributions of the fixed effect to *z*,

u is an random, unknown column vector of length q, with zero means, giving the contribution of the random effect to *z*,

e is an random, unknown column vector of length n, with zero means, giving the residual contribution to *z*,

X is a known *n* x *p* design matrix (with zero and one entries) which assigns the fixed effects to individuals, and

Z is a known *n* x *q* design matrix (with zero and one entries) which assigns the fixed effects to individuals.

Focusing just on the column vectors and expressing them as their transposes, they are

$$\begin{aligned} z^T &= (z_1 \quad z_2 \quad z_3 \cdots z_n), \\ b^T &= (b_1 \quad b_2 \quad b_3 \cdots b_p), \\ u^T &= (u_1 \quad u_2 \quad u_3 \cdots u_q), \\ e^T &= (e_1 \quad e_2 \quad e_3 \cdots e_n). \end{aligned}$$

Similarly, the matrices are

$$X = \begin{bmatrix} X_{11} & X_{12} & \cdots & X_{1p} \\ X_{21} & X_{22} & \cdots & X_{2p} \\ \vdots & \vdots & \ddots & X_{n-1p} \\ X_{n1} & X_{n2} & X_{np-1} & X_{np} \end{bmatrix}$$

$$Z = \begin{bmatrix} Z_{11} & Z_{12} & \cdots & Z_{1q} \\ Z_{21} & Z_{22} & \cdots & Z_{2q} \\ \vdots & \vdots & \ddots & Z_{n-1p} \\ Z_{n1} & Z_{n2} & Z_{np-1} & Z_{nq} \end{bmatrix}.$$

The second part of the model has to do with the distributions of the unknown random variables, *u*, which will usually be closely related to breeding values, *x*, and *e*, which has the same meaning it did in [5.4] . We will denote the variance-covariance matrix for a vector of random variables as VAR, which describes the theoretical sampling variance that would arise if we made repeated draws from our statistical population. VAR(*u*) = *F* is a *q* x *q* symmetric matrix that is usually nonsingular (has a matrix inverse). We wish to estimate *F*, because from it and *Z* we can obtain an estimate of *G*, the genetic variance of the trait. Commonly, the values of *u* will not be independent (e.g., when individuals are related) and we can take that non-

independence into account in specifying the structure of the unknown matrix *F*. Likewise, VAR(e) = *R*, is an *n* x *n* symmetric matrix that is usually non-singular. Usually we will assume that the errors, e, associated with each individual are independent, so that all the elements in VAR(e) are zero. The vectors *u* and *e* are also commonly assumed to follow multivariate normal distributions, and likelihood expressions are based on that assumption.

Although *F* and *R* are unknown matrices, in general we will know or can assume something about each of their structures. For example, the random variables *u* of two related individuals are not independent, but if we know the pedigree of those individuals, we could use their relatedness to compute an appropriate value for a particular element of *F*. *R* will often be a diagonal matrix (with zeros for off-diagonal elements), but errors that are correlated between individuals could also be accounted for.

Turning to the item of key interest, how can we use the animal model to estimate the genetic variance of the trait? Consider the simple case in which the random effects, *u*, are parts of breeding values, which each individual inherits from a different, unrelated sire. Then

$$F = VAR(u) = I\sigma_s^2$$

$$= \begin{bmatrix} 1 & 0 & \cdots & 0 \\ 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \sigma_s^2 = \begin{bmatrix} \sigma_s^2 & 0 & \cdots & 0 \\ 0 & \sigma_s^2 & \cdots & 0 \\ \vdots & \vdots & \ddots & 0 \\ 0 & 0 & 0 & \sigma_s^2 \end{bmatrix},$$

where σ_s^2 is the component of variance among sire effects, which needs to be estimated. Each individual inherits half of its breeding value from its sire, $u = \frac{1}{2}x$, so the variance of those halves is ¼ *G*. In other words, $2u$ estimates *x*, the vector of breeding values, and $4\sigma_s^2$ estimates *G*, the genetic variance of the trait. Similar principles apply in more complicated cases. For example, if sires are related, a sire relationship matrix (with relationship coefficients for pairs of sires as elements) replaces *I* in the expression above, but σ_s^2 is still the key quantity that leads to an estimate of *G*.

Given the model just specified, we also have expressions for the trait mean and its sampling variance. The expected value, or mean, and variance of the trait are

$$E(z) = Xb$$
$$VAR(z) = ZFZ^T + R.$$

We are not surprised to see that the trait mean is a function of the fixed effects, because we have standardized the random effects means so that they are zero. The sampling variance-covariance of the mean is a function of the sampling variance-covariance of random effects, ZGZ^T, and residual contributions, *R*.

The point of the animal model, with all of its matrix and vector book-keeping, is that it can be used to estimate the unknown breeding values, *x*, and their variance, *G*, together with their sampling properties, while accounting for one or many kinds of fixed effects. At the same time,

the model estimates the values of fixed effects. All of these outputs can be very much worth the effort of setting up the precursor tables to *Z* and *X* that are required by estimation programs. Details of implementing the animal model are discussed by Meyer (2007), Hadfield (2010 = MCMC Methods …). Furthermore, the approach can be extended to multiple traits, as we shall see in the next chapter.

Pedigree methods for estimating *G* and *x* have become increasingly flexible but have not escaped some key assumptions of normality. The original specifications of the animal model assumed that the distribution of the phenotypic trait, *z*, was multivariate normal, as well as the breeding values, *x*, and residual effects, *e*. These distributional assumptions allowed likelihood functions to be specified in Gaussian terms, and the maxima of those functions could found by analytical manipulations (Thompson 2008, Meyer 2007). More recently, Markov chain Monte Carlo (MCMC) methods allow one to maximize complex likelihood functions and so escape from the assumption that *z* is normally-distributed (Sorenson and Gianola 2002, Hadfield 2010). These methods employ a link function (Nelder and Wedderburn 1972), so that the animal model is specified in terms of a derived variable, rather than *z*. The derived variable can take any of a variety of specified distributional forms (Gaussian, Poisson, binomial, etc). Random effects can include interactions, and fixed effects may be continuous as well as categorical. Random, fixed and residual effects are assumed to be multivariate normal with specified covariance structures. See Hadfield (2010) for an illuminating worked example.

5. 443 Estimation of genetic variance using the genomic approach

The genomic approach is based on the success of genome-wide association studies (GWAS) in finding statistical associations between single-nucleotide polymorphisms (SNPs) and human diseases and other phenotypic traits (Hindorff et al. 2009). In this genomic approach, a linear model is used to estimate *G* as a function of the additive effects of numerous SNPs and a relationship matrix which is estimated from the SNP data (Yang et al. 2010, 2011a, 2011b). The triumph of the genomic approach is that while simply summing the univariate contributions of individual GWAS (see Fig. 5.0a) accounts for only a small fraction of *G* (as estimated by covariance or standard pedigree methods), simultaneous estimation accounts for a much larger fraction. The implication is that hundreds of genes of small effect contribute to the heritability of stature in humans (refs).

Despite the triumph of the genomic approach in accounting for the heritability of stature and other human traits, the estimates fall short of covariance estimates, a substantial amount of heritability remains 'missing'. In contrast, in cattle and Soay sheep, genomic and covariance estimates are in close agreement (Berenos et al. 2014). Berenos et al. (2014) argue that the discrepancy may arise because effective population size is smaller in the cattle and sheep populations, so that linkage disequilibrium (LD) between causal loci and SNPs is higher. As a consequence, LD and the presence of close relatives in those samples leads to higher estimates of heritability.

5.444 Technical issues in estimating additive genetic variance

Complications arise in estimation because of the special nature of some traits. For example, some traits change as a function of age, size is a conspicuous example. One solution is to define age-specfic traits and take measurements at specified intervals of age. Alternatively, age can be

treated as a fixed or random effect using the animal model. If inheritance of the age-trajectory is the issue, the trajectory itself can be considered a trait in the function-valued approach (Kirkpatrick and Heckman 1989, Gomulkiewicz and Kirkpatrick 1992, Meyer and Hill 1997, Kingsolver et al. 2001). The theory for function valued traits also applies to reaction norms in which phenotype expression varies as a function of an environmental variable.

The expression of some traits fluctuates through time. Courtship displays, heart rate, and body temperature are examples. If the trait value for an individual for such a trait is captured by a single measurement, the trait is bound to have a small heritability. From an ecological or evolutionary perspective, this small heritability may be misleading if the trait is expressed thousands or even millions of times during the individual's lifetime or during relevant selection episodes. One solution is to define the trait as the sum or average of some fixed number of measurements. One can readily show that both the repeatability and the heritability of the trait is an increasing function of the number of measurements (Arnold 1994).

5.445 Survey of heritability estimates

A survey of heritability estimates for morphological characters reveals a broad distribution centered in the range 0.4-0.5 (Fig. 5.6). One might be tempted to conclude from this survey, as some authors have in the absence of data, that everything is heritable. On reflection, that conclusion is unjustified for on several grounds. In the first place, Fig. 5.6 reports point estimates, while ignoring sampling properties. Secondly, publication bias undoubtedly inflates the left-hand side of the distribution, since statistically nonsignificant estimates may not be published as frequently as significant estimates. Finally, when we approach the problem from a multivariate perspective in the next chapter, we will find that heritable variation is so sparse as to be completely lacking in some regions of phenotypic space.

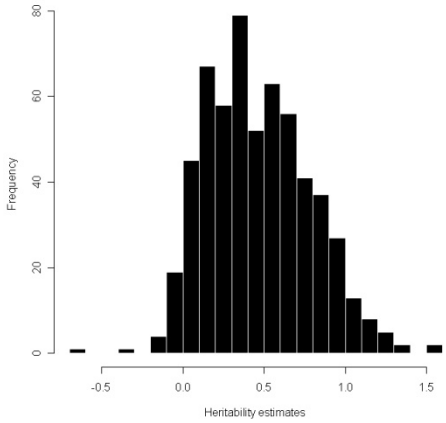
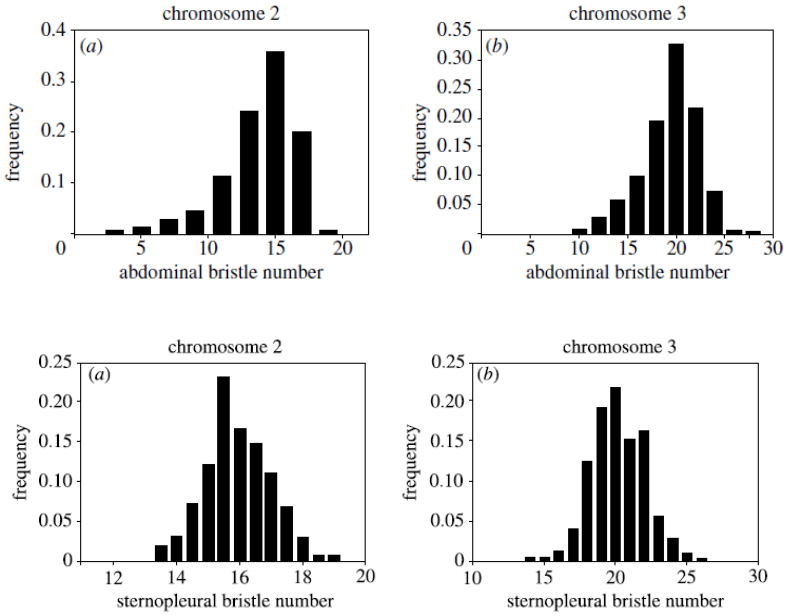


Figure 5.6. Histogram of a large sample (n=580) of heritability estimates for morphological characters in vertebrate and invertebrate animals. Based on data in Mousseau & Roff (1987), courtesy of D. Roff. Note that estimates outside the parameter range ($0 \le h^2 \le 1$) are possible with some estimation procedures. Mean = 0.47, median = 0.44, variance = 0.10.

5.45 Detailed analysis of quantitative variation within populations

Because the genetic basis of natural variation in *Drosophila* bristle counts has been studied in depth from a number of perspectives, the lessons from this case study are especially informative (Mackay & Lyman 2005). Two overarching conclusions spring from the long tradition of work on this study system. First, certain results are consistent from study to study, even as increasingly sophisticated techniques are brought to bear. Second, the nature of quantitative variation appears to be more complex, the more we study it.

Figure 5.zz. Distributions of bristle counts among chromosome substitution lines derived from a single natural population of *Drosophila melanogaster*. From Mackay & Lyman (2005).



Additive genetic variation is consistently abundant for counts of both abdominal and sternopleural bristles. Estimates of heritability are consistently about 0.50 for both traits and are largely attributable to additive genetic variance (Mackay & Lyman 2005). For example, an early study by Clayton et al (1957) estimated the heritability of the abdominal count using three different covariances (offspring-parent, paternal half sib, full sib) with similar results (0.51±0.07 s.e., 0.48± 0.11 s.e., 0.53±0.07 s.e.). The similarity of the offspring-parent and full sib estimates to the half sib estimate indicates that most of the genetic variance is additive. … compare with Coyne & Beecham (1987) … responses to deliberate selection practiced on a base population … increasing sophistication in the characteristics of the base population … ranging from hapzard formation of a population maintained in a population cage to careful sampling of scores or hundreds of isogenic lines sampled from a single natural population … QTL linkage mapping of differences in divergent, selected lines … samples of single chromosomes from a single natural population, and perpetuated in chromosome substitution lines (Mackay & Lyman 2005) … the resulting histogram portray the contribution to the standing crop of variation is by particular chromosomes (e.g., chromosomes 2 and 3). Notice that the variance among chromosomes of a particular type (i.e., 2 vs 3) is substantial (Fig. 5.zz)

A picture of increasingly complicated genetic architecture has also emerged as ever more sophisticated techniques have used to analyze genetic variation in *Drosophila* bristle numbers and other quantitative traits. In the first place, the *Drosophila* experience strongly reinforces the long-held view of quantitative geneticists that the more a trait is studied, the larger the number of loci that are discovered. Noting the steady climb in the number of loci found to affect bristle numbers as the resolution of QTL mapping studies improves, Mackay & Lyman (2005) concluded that over 100 loci potentially affect these counts. The distribution of contributions from these many loci appears to be normally distributed about zero, as we shall see in section 5.q {on mutational input}. Aside from the multiplicity of contributions, complexity also arises from a number of other sources: sex-specific effects, environment-specific effects, and epistasis. All of these complications are abundantly documented in the inheritance of bristle counts and many

other quantitative traits in *Drosophila* (Mackay & Lyman 2005, Mackay 2009 = 3rd int cong quant gen).

5.50 Theoretical input from mutation

Models that specify how much new genetic variation in contributed by mutation each generation typically have two ingredients: a mutation rate (per haploid locus per generation) and a distribution of mutant (allelic) effects with specified variance for individual loci. We shall discuss Kimura's (1965) infinite-alleles mutation model because it leads to a powerful treatment of equilibrium between mutation and stabilizing selection. According to this model, each of *n* freely-combining loci affecting the trait of interest can produce an infinite sequence of new alleles by mutation. That is to say, each new mutation is different from all that preceded it. The effects of the mutations on the trait are additive. If we also assume that the mutational effects are small, Kimura's model predicts that the equilibrium distribution of allelic effects is approximately Gaussian (Latter 1970, Lande 1975). Let μ be the mutation rate per haploid locus per generation, and let the distribution of mutant allelic effects (i.e., average effects, α) be identical at each locus with a mean of zero and a variance denoted as α^2. From these assumptions, it follows that the per generation input from mutation to variance in the trait is

$$U = 2n\mu\sum\alpha^2 = \zeta M ,$$

where $\zeta = 2n\mu$ is the total mutation rate, and *M* is the variance in mutational effects summed across all loci (Lande 1975, 1977). In a model of mutation-selection balance, this per generation input from mutation to the genetic variance of a trait, *U*, is balanced by losses due to stabilizing selection.

5.51 Mutation-selection balance

Despite broad agreement that a balance between mutation and stabilizing selection is a plausible mechanism to account for the maintenance of genetic variation in continuously-distributed traits, the details of the process are still open to debate. The long standing view that heritable variation is abundant for most morphological traits is strongly supported by recent literature reviews (section 5.x). Likewise, the prevalence of stabilizing selection and its ability to account for trait stasis has long been recognized (Haldane 1932, Wright 1935, Simpson 1944, Schmalhausen 1949, Lewontin 1964, Charlesworth et al. 1984). The problem with stabilizing selection is that it nibbles away at genetic variation, even though it stabilizes the trait mean. Lande (1975) argued that polygenic mutation was capable of compensating for the variation eroded by stabilizing selection and showed that a mutation-selection balance (MSB) was consistent with data on both selection and mutation. Lande's argument was based on particular assumptions about mutation and selection, so one can ask how sensitive the conclusions are to those assumptions. One can also ask whether other sets of assumptions might account for the maintenance of variation while also accounting for related phenomena. The upshot of these considerations is that while Lande's (1975) proposal does a reasonable job of accounting for the maintenance of genetic variation, other more complicated sets of assumptions do at least as good a job on the maintenance score, while simultaneously accounting for more of the known features of polygenic mutation. At the same time, decisions about which assumptions to prefer are complicated by the fact that

empirical data are still sketchy on the issue of how mutational effects are distributed. In Lande (1975) and the MSB models discussed below, stabilizing selection is modeled as a Gaussian function (3.07), with width parameter ω.

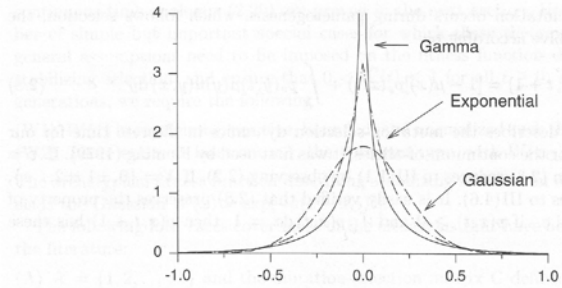


Figure 2.1 Three different mutation distributions serving as candidates for u_{RW}, u_{HC}, and u_{ZC}. All have variance $\gamma^2 = 0.05$. The dahsed line represents a Gaussian distribution (kurtosis = 0), the dash-dotted line represents an exponential distribution reflected about zero (kurtosis = 3), and the solid line a Γ-distribution reflected about zero with $\theta = \frac{1}{2}$ (kurtosis = 26/3).

The amount of genetic variation that can be maintained by mutation-selection balance is affected by the form of the distribution of mutational effects. {for this discussion see especially the accounts given by Slatkin & Frank 1990 and Burger 2000} In an earlier section (5.x) we pointed out that Lande's (1975) model, based on Kimura's (1965) infinite alleles model of mutation, implies that the equilibrium distribution of allelic effects at each locus is Gaussian. Other statistical models of mutation have been proposed (e.g., Crow & Kimura 1964; Kingman 1977, 1978; Zeng & Cockerham 1993) and they can lead to quantitatively different predictions about how much genetic variation can be maintained {Figure 2.1 from Burger 2000, showing reflected gamma, exponential and Gaussian distributions of allelic effects}. Burger's (2000) synthesis provides a useful summary of an extensive theoretical literature. One simplifying result is that linkage relationships among loci have little effect the equilibrium genetic variance in large populations. Consequently, single-locus results can be extrapolated to yield multiple locus conclusions. The Gaussian set of assumptions about mutation asserts that mutational effects are small relative to the single-locus genetic variances at equilibrium. The consequence is that most genetic variance arises from rare alleles of large effect. Under this view of mutation a variety of mathematical approaches predict that the equilibrium genetic variance is approximately $2U\omega$ (Lande 1975, Fleming 1979, Burger 2000). Alternatively, if one assumes … house of cards model of mutation (Kingman 1977, 1978) ... the equilibrium genetic variance is approximately $\sqrt{U\omega}$ (Turelli 1984, Burger 2000).

A fundamentally different model of selection and mutation was proposed by Robertson (1960). In this view, stabilizing selection arises from deleterious mutations that are disproportionally represented in genotypes that reside at the two ends of the trait distribution. According to this model, each mutation has two effects, one on the trait and the other on fitness itself. The trait can be viewed as selectively neutral or, in a generalization by Zhang & Hill (2002), as experiencing pure stabilizing selection, as well as the *apparent stabilizing selection* induced by the pleiotropic effects of mutant alleles on fitness. Whatever the merit of Robertson's proposal, Zhang & Hill (2002) found that apparent stabilizing selection made a relatively small contribution to the genetic variance that was maintained at equilibrium.

Contemplating the concept of apparent stabilizing selection leads us to consider the effects of mutations on fitness and to include them in a model of mutation-selection balance. One well established result is that most mutations are deleterious and tend to be recessive (Mukai et al 1972, Simmons & Crow 1977, Charlesworth 1979, Mackay et al 1992, Caballero & Keightley 1994, Keightley & Lynch 2003). Furthermore, partial dominance appears to be

common in the inheritance of continuously-distributed traits (Fig. 5.x). For both of these reasons, Zhang et al. (2004) included dominance in their investigation of mutation-selection balance, which used a joint-effect model that included both pure and apparent stabilizing selection, as in Zhang & Hill (2002). In line with some empirical results, Zhang et al. (2004) assumed that the distributions of allelic effects on the trait, $|a|$, and on fitness were more leptokurtic than a normal distribution and modeled them with with gamma distributions. Their general conclusion is that the inclusion of dominance in the model leads to the maintenance of a quantitatively higher level of additive genetic variance at equilibrium. In other words, a model without dominance leads to a conservative prediction about the maintenance of genetic variation.

Returning to our main theme of characterizing the opposing roles of stabilizing selection and mutation in maintaining genentic variation, we shall now focus on the results of the Gaussian model of allelic effects in a completely additive framework (no dominance or epistasis), not because this is the only possible model, but because its results are in broad agreement with more complicated - and perhaps more realistic - models. Stabilizing selection reduces the standing crop of genetic variation within a generation by an amount given by

$$\Delta_s G = G^2(\gamma - \beta^2)$$

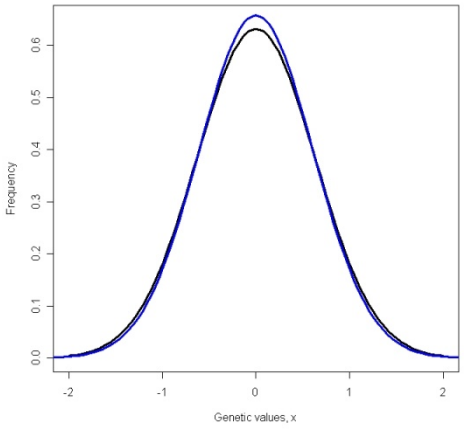
(Lande 1975, 1980; Phillips & Arnold 1989). At equilibrium, the losses due to selection are balanced by the input from mutation and recombination, so that

$$U = \zeta M = -\Delta_s G$$

(Lande 1980a). If both the phenotypic distribution, *p(z)*, and the ISS are Gaussian, we can show that the equilibrium genetic variance is a function of the input from mutation and the curvature of the AL,

$$\hat{G} \cong \sqrt{U\tilde{\omega}}\,,$$

where $\tilde{\omega} \equiv \omega + E \cong \omega + P$ (Lande 1975, 1977, 1980a). In particular, we see - as expected - more genetic variance at equilibrium when mutational input is large and stabilizing selection is weak (large ω). Substituting realistic values for G and γ, we see that the effect of stabilizing selection in diminishing genetic variation and corresponding restorative power of mutation are both relatively weak.



Even when stabilizing selection is relatively strong, the amount of genetic variation lost each generation due to selection and restored by mutation is small. For example in Figure 5.9, the curves show hypothetical distribution of genetic values before selection (blue; G=0.400) and after selection (G*=0.368), when stabilizing selection is relatively strong, ($\gamma = -0.2$, and $\beta = 0$). In an equilibrium population, mutation would restore variation to blue curve in the next generation.

Empirical tests of MSB models consistently show that with a simple additive genetic model of inheritance mutation can not keep pace with realistic levels of stabilizing selection …

5.52 The mutation process as revealed by mutation accumulation experiments

It is a remarkable fact that mutation alone can supply enough genetic variation to sustain appreciable response to selection in polygenic traits … mutation accumulation (MA) experiments … mutational input to variation in the abdominal and sternopleural bristle counts of *Drosophila* has been analyzed with MA experiments … starting from an inbred stock population, Mackay et al (2005) established replicate lines and subjected each to truncation selection for high or low bristle counts for 206 generations … All of the selection lines showed appreciable responses in the anticipated directions (Figure 5.xx). According to a model of mutation in which effects are additive and symmetrically distributed, we would expect to see symmetrical responses to selection in both characters (Hill 1982), which is certainly not the picture we see in Fig. 5.xx. Instead, both traits show asymmetrical responses, with abdominal bristles showing a greater response in the downward direction, while sternopleural bristles show a greater response in the upward direction. If effects are additive, these results suggest that a preponderance of positive mutations in sternopleural bristles, and a preponderance of negative mutations in abdominal bristles. Of course, a variety of other interpretations are also consistent with the results. MA experiments can also be used to estimate mutational variance. Using the infinitesimal model and averaging over all 206 generation and both traits, the average estimate of mutational variance, M, is 3.15×10^{-3} ($\pm 0.24 \times 10^{-3}$ se). Standardizing by the environmental variances, the average estimate of M/E is 0.24×10^{-3} ($\pm 0.03 \times 10^{-3}$ se). The latter estimate is consistent with earlier estimates for these characters (Fig. 5.xy).

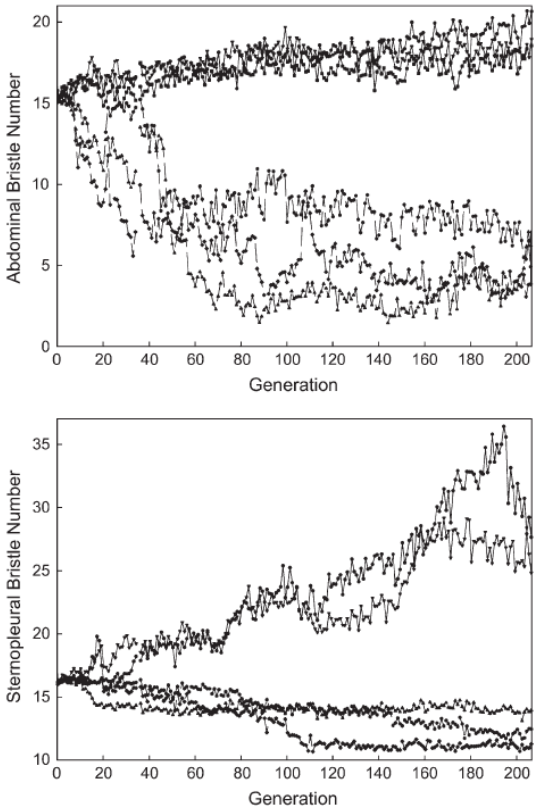


Figure 5.xx. Responses to deliberate selection for increased and decreased bristle counts in *Drosophila melanogater*. Replicate lines were established from an inbred base population so that any responses to selection would be based on mutational input. (a) Upper panel, responses to selection on abdominal bristle counts. (b) Lower panel, responses to selection on sternopleural bristle count. From Mackay et al (2005).

5.53 Estimates of mutation input to trait variance

Estimates of standardized mutational variance consistently fall in the range … (Lynch 1988, Halligan & Keightley 2009 – see their Table1). *use Lynch & Walsh 1998 table for mutational heritability, which they call Vm/Ve, or in the notation used in this chapter, U/E * These results imply that for a trait in which heritability is approximately 50%, so that G ≈ E, approximately a thousand years would be required to build genetic variance up to that level just by mutation

Mutation rate ... {see Lynch 2010 on the scaling of mutation rate with genome size and Ne ... may need to create a second section since these data are from genome sequencing ... see Lynch 2009b for summary of recent results on human genome ... see Denver et al 2009 on genome wide sequencing results for mutation rates in MA lines of C elegans ...see Denver et al 2004a on the details of mutations in C elegans MA lines = examples of nucleotide substitutions and their rates ... see Azevedo et al 2002 on mutation rate for body sized estimated from MA lines in C elegans ... asymmetrical distribution of lines means and asymmetry in response to selection}

Table 5.xx. Estimates of standardized mutational variance (Lynch & Walsh 1998).

Species	Character	U/E ($x10^{-3}$)	Reference
Drosophila melanogaster	Abdominal bristle number	3.5	See Lynch & Walsh 1998
	Sternopleural bristle number	4.3	See Lynch & Walsh 1998
	Ethanol resistance	0.9	Webber & Diggins 1990
	Body mass	4.7	Clark et al. 1995
	Wing dimensions	2.0	Santiago et al. 1992
	Viability	0.3	See Lynch & Walsh 1998
Tribolium castaneum	Pupal mass	9.1	Goodwill & Endfield 1971
Daphnia pulex	Life-history traits	1.7	Lynch 1985
Mouse	Lengths of limb bones	23.4	Bailey 1959
	Mandible measures	23.1	Festing 1973
	Skull measures	5.2	See Lynch & Walsh 1998
	6-week mass	3.4	Caballero et al. 1995
Arabidopsis thaliana	Life-history traits	3.9	Schulz et al. 1999
Maize	Plant size	11.2	Russell et al. 1963
	Reproductive traits	7.3	Russell et al. 1963
Rice	Plant size	3.0	Oka et al. 1958
	Reproductive traits	2.8	Sakai & Suzuki 1964
Barley	Life-history traits	0.2	Cox et al. 1987

The statistical properties of the new mutants that arise in mutation accumulation experiments can be characterized. In a particularly revealing study, Dilda & Makay (2002) selected on abdominal and sternopleural bristle numbers, starting with a highly inbred line which was initially free of P-elements. After producing high and low lines by truncation selection, Dilda & Mackay extracted single chromosomes from each selected line and perpetuated them in isogenic lines. Using interval mapping to determine genomic positions of brisle count QTLs, they characterized 33 QTLs for sternopleural bristle number, 31 for abdominal bristles, 11 that affected both phenotypes … the combined distributions of additive and domimance effects are

shown in Figures ww aa Fig 6 = distribution of additive effects … Fig 8 = distribution of dominance effects …

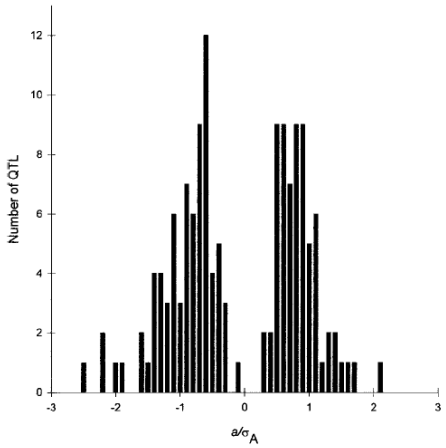


FIGURE 6.—Distribution of additive QTL effects.

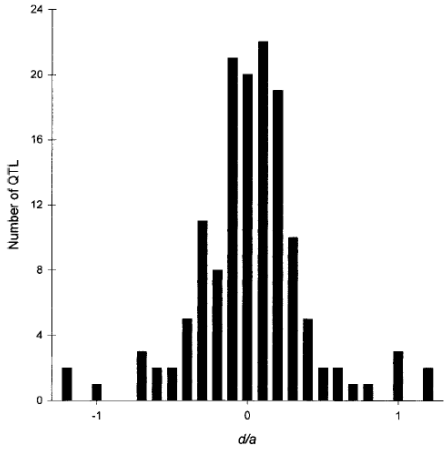


FIGURE 8.—Distribution of degrees of dominance of QTL.

These results indicate that distribution of allelic effects supplied by mutation is approximately normal and with no overall bias in dominance.

{Redraw these two histograms and superimpose normal distributions, with means of zero and variance fitted by eye. In captions note that the standardized properties of QTLs are summed over traits, sexes, etc}

The expression of mutations that affect polygenic traits is imbedded in a complicated developmental network that stretches from the genome to the expressed phenotype. … the genotype-phenotype map …the molecular basis for input from mutation {see papers by Denver, Baer, etc – might start with account in Freeman & Herron} …

5.54 The mutation process as revealed by effects of P-element mutagenesis on bristle numbers in *Drosophila*

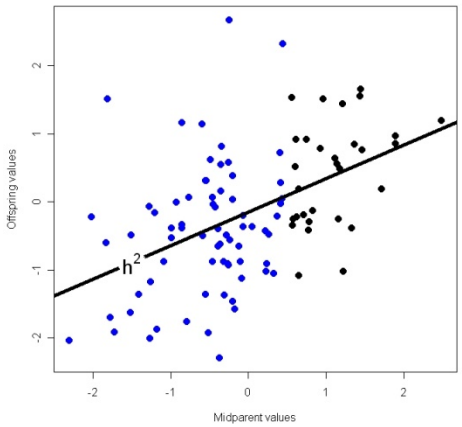
Special techniques to study the statistical properties of new mutations are available in *Drosophila melanogaster*. In particular, P- element mutagenesis takes advantage of the special properties of transposable elements to create stable lines that contain one or a few new mutations on particular chromosomes (Robertson et al 1988). In specially created lines, the rate of P-element transposition occurs at a particularly high rate (two inserts per chromosome per generation), so that properties of even rare mutational events (i.e., rare alleles of large effect) can be characterized (Mackay et al. 1992). Furthermore, the statistical properties of P-element inserts mimic the natural mutation process. Indeed more than 50% of natural mutants in *D. melanogaster* represent P-element insertions (Finnegan 1992). Starting with a highly inbred host strain that is initially free of P-elements, replicate lines are produced that differ only in P-element insertions. The effects on these now stable insertions (QTLs) on particular phenotypes such as bristle counts can then be characterized.

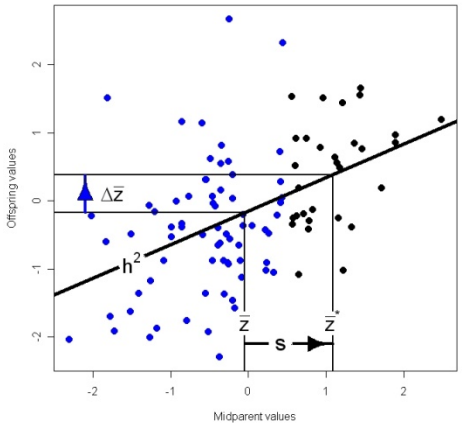
Analyses based on P-element mutagenesis reveal that mutations at possibly hundreds of loci affect numbers of abdominal and sternopleural bristles. Two teams of investigators created nearly 2800 P-element insertion lines (Lyman et al 1996, Spradling et al 1999). Analysis and mapping of these two sets of lines revealed, respectively, 42 and 262 loci that affect bristle numbers (Norga et al. 2003). A substantial fraction of the loci identified in both screens are involved in neurogenic processes.

Chapter 9: Response of a Single Trait to Selection

Overview.- The per generation response of the trait mean to directional selection is a function of genetic variance and the magnitude of selection. Experimenters have imposed deliberate selection for many generations to improve domesticated plants and animals and to gauge response in experimental lines. Steady change in the mean has often been observed for 10-120 generations, although sometimes the response is asymptotic. These observations reinforce the view that abundant genetic variation is usually available for most kinds of traits, even in small populations exposed to intense selection. The genetic underpinnings of selection response have been assessed in studies of quantitative trait loci (QTLs). One observation is of special significance, the distribution of QTLs appears to be skewed to the left.

9.0 Response to selection as a regression problem.
In Chapter 1 we considered the effects of selection within a generation. We now wish to consider how those effects are transmitted from one generation to the next. Consider the plot of offspring averages as a function of parental averages in Fig. 9.0a. The regression of offspring means on parental means is equivalent to a regression of breeding values on phenotypic values or $GP^{-1} = h^2$, the slope of the line in Fig. 9.0a. That figure also shows the implementation of a truncation selection scheme in which we suppose that only midparents with a value of ≥ 0 are allowed to breed and become the actual parents of the next generation. A result due to Pearson (190x), tells us that if we select on one trait, call it *x*, that selection may change the variance of *x*, the variance of a correlated trait *y*, and the covariance of *x* and *y*, but it will not change the regression of *y* on *x*. Consequently, the regression of breeding values on phenotypic values for the set of selected parents in Fig. 9.0a is h^2, the same as it is in the entire set of potential parents. The upshot of this result is that we can with justification draw the regression plot, as in Fig. 9.0b, so that the difference in average breeding values caused by the selection differential *s*, is a regression. Furthermore, we can equate the difference in breeding values of actual and potential parents with an induced difference in phenotypic values in the next generation. In other words, the change in phenotypic mean in the next generation caused by selection, the *response to selection*, is





$$\Delta\bar{z} = GP^{-1}s = h^2 s \,. \quad (9.00)$$

Figure 9.0. Response to selection as a regression problem. (a) A plot of hypothetical mid-offspring values and a function of hypothetical mid-parental values, showing h^2, the slope of the regression line (heavy line). (b) Truncation selection acts so that one set of parents (points shown in black) becomes the actual parents of the next generation. Their trait mean is $\bar{z}^*$, whereas the mean of all potential parents (blue and black points) is $\bar{z}$. The vertical lines project those means up to the regression, which yields the two expected offspring means (horizontal lines), and hence the expected response to selection, $\Delta\bar{z}$.

We see how this equation describes the response to truncation selection, but it also describes the response to whatever form of selection is associated with a directional selection differential of magnitude *s*. If $GP^{-1} = h^2$ remains constant through time, and the same selection differential, *s*, is applied generation after generation, after *t* generation we expect the accumulated response to selection to be

$$\Delta\bar{z}_t = tGP^{-1}s = th^2s \quad (9.01)$$

Even miniscule directional selection, if long continued, can produce huge effects. Suppose that the same slight selection differential, s=0.01, is applied generation after generation for 6,000 generations, the approximate elapsed time since … modern humans … A selection differential this small would not be detectable in field studies. Nevertheless, with a typical heritability of 0.4, the trait mean would increase by 24 phenotypic standard deviations in that amount of elapsed time … On shorter time scales, a hundred or a thousand times smaller, the power of directional selection has been established by plant and animal breeders, as we shall see in section (9.x)

9.1 Response to selection in a set of replicate populations of finite size

The response to selection in (9.00) is the so-called deterministic response, the change we expect in a population of infinite size or the average response we expect to see across a series of replicate populations of finite size. Both selection and drift can happen each generation within a lineage so that their effects are combined in the total per generation change in $\bar{z}$. For example, each generation we can model the response to selection with (9.00) and then draw an random sample of parents from a normal distribution with mean zero and variance G/N_e to yield a change in the mean after selection due to drift. Adding that stochastic change in the mean to the deterministic change due to selection gives us, each generation, the combined effects of selection and drift. If we start a set of finite replicate populations at generation 0 with the same zero mean, their trajectories through time form a cone around the deterministic response, th^2s (Fig. 9.1). The smaller the effective size, the wider the cone at any generation *t*. In other words, response to selection is not a simple 'march of the frequency distribution'. When populations are of finite size, as they must be in the real world, stochastic dispersion of means is superimposed of the simple deterministic march the mean of means.

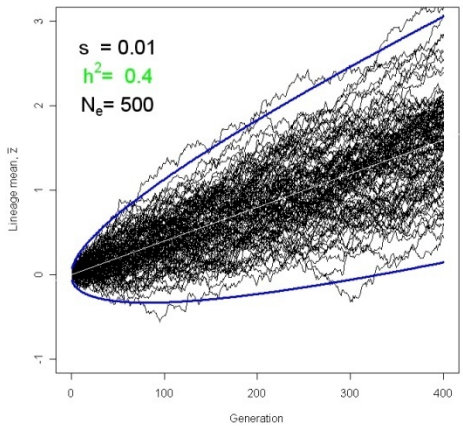


Figure 9.1 Response to selection in a set of replicate populations of finite size. In the simulations depicted here, 100 lineages of moderate size ($N_e = 500$) respond to a very slight directional selection (s=0.01) for 400 generations. The trajectories of the lineage means (shown in black) reflect both response to selection and drift. The deterministic response to selection is shown as a white line. The 99% confidence limits for the overall lineage mean are shown with blue lines.

9.2 Response to deliberate selection in the laboratory…{plenty of studies of dir seln… a few examples, e.g., Tribolium body size over >100 generations … but ck also studies of double truncation seln and other schemes intended to change trait var} … Fig. 9.2 = Examples of long term response to deliberate selection on body size in *Drosophila*, *Tribolium* and mice.

9.3 Response to deliberate selection in plant and animal stocks ... include a summary table show how much mean was shift as a function of trait, number of generations of selection

9.4 Response to selection in natural populations

… Galapagos finches … Fig. 9.3 Response to natural selection in finch beaks … other examples from Hendry and others

9.5 Minimum selective mortality

It is useful to consider the minimum amount of selective mortality required to account for known divergence event, because the requisite data to do the calculation are readily available. Suppose we know or can infer the means of a normally-distributed trait at two points in time, separated by *t* generations. How strong must truncation selection be each generation to account for observed magnitude of divergence (difference in means) on that time scale? Let the mean of the distribution before selection each generation be $\bar{z}$ on a scale in which the within-population phenotypic standard deviation is 1, with the point of truncation located at $\bar{z} - b$. Using expression (9.00), we can show that the expected change in the mean each generation resulting from this mode of selection is

$$\Delta\bar{z} = \pm \frac{G}{\sqrt{2\pi P}} \exp(-b^2/2).$$

If we accumulate this reponse to selection for *t* generations and equate it with the absolute value of the observed divergence in mean, we have

$$\left|\bar{z}_t - \bar{z}_0\right| = \frac{tG}{\sqrt{2\pi P}} \exp(-b^2/2),$$

where $\bar{z}_0$ and $\bar{z}_t$ are, respectively, the trait means at generations 0 and *t*.

Solving for the truncation point, we obtain

$$b = \pm\sqrt{-2\ln(\sqrt{2\pi P}\,\frac{\left|\bar{z}_t - \bar{z}_0\right|}{tG})}$$

Lande (1976). In other words, if we set the truncation point at distance *b* from the mean and suppose that all individuals beyond that point die, and repeat this procedure for *t* generations, we can account for the observed divergence.

Surprisingly weak truncation selection is required to account for particular cases of divergence that are observed in the fossil record. Assume a standard value for G (0.5), with *P*=1. Lande (1976) analyzed 21 cases of divergence in mammalian tooth dimensions from the fossil record. Divergence ranged from 0.8 to 44 phenotypic standard deviations over time intervals ranging from 0.3-17 million generations. In all cases the observed divergence could be accounted for by truncation selection of a magnitude of 10^{-6} to 10^{-7} per generation. In other words, only one in ten million to one in a million individuals would have to die a selective death per generation to account for these instances of divergence. Of course, the magnitude of selection is small in part because the deaths are spread out over the entire extent of the elapsed time interval. But even if we imagine that the selective deaths occurred during a fraction of the total time available in each interval, the magnitude of necessary truncation selection is still very small.

9.6 The distribution of genetic effects accumulated during a response to selection

What kinds of genetic (allelic) effects contribute to the responses to selection that we have just reviewed? More precisely, what is the distribution of effects of those genes that are selection to fixation during a bout of adaptation? Could those effects simply be a random sample of mutations so that the distribution we seek resembles the distribution of mutational effects? This answer seems unlikely because upon reflection we realize that an allele of large favorable effect might be rapidly swept to fixation, so that such genes would be disproportionally represented. Clearly we need a model.

A simple model of selection during a bout of adaptation is one in which an intermediate optimum has suddenly moved to a new position some distance from the phenotypic mean. In a later chapter we will refer to this situation as the *displaced optimum model* and consider its consequences in some detail. For now, we simply need to specify that the selection regime that provokes adaptation is an instantaneous displacement of the optimum of a Gaussian ISS. Given that this event has occurred, what kinds of alleles will be swept to fixation during the time it takes for the phenotypic mean to evolve to the new position of the optimum?

Orr (1998, 1999) has modeled and simulated the process just specified to determine the distribution of genetic effects that become fixed during the approach to the new optimum. This problem has an interesting conditional effect. Whether a particular allele is favorable or not depends on its effect size and the distance from the phenotypic mean to the optimum. Early in the process of adaptation, alleles with large effect may be favored, but when the mean is closer to the optimum, alleles of smaller effect will be favored, because they will not cause the population to overshoot the optimum (Fisher 1930, Kimura 1983). Orr (1998) was able to show that the proportional reduction in the distance to the optimum by each expected mutational substitution is nearly a constant. Secondly, the distribution of effect sizes for the mutations that are fixed during approach to the optimum is approximately negative exponential (Fig. 9.qq). Furthermore, this distribution holds regardless of how many trait dimensions are involved in the displacement of the optimum. Finally and most importantly, the distribution is negative exponential regardless how mutational effects are distributed.

Orr's (1998, 1999) exponential result has important implications for our understanding of the genetic differences that accumulate during adaptation. Our first expectation is that the process should be polygenic. On a probabilistic basis, we would not expect the first mutation to take the phenotypic mean all the way and exactly to the optimum. Instead, we expect mutant alleles of various effect sizes to be swept to fixation. Secondly, while a few genes may be of large effect, we expect that most will be of intermediate and small effect. In the next section we will consider QTL analysis, an empirical approach that will test these expectations.

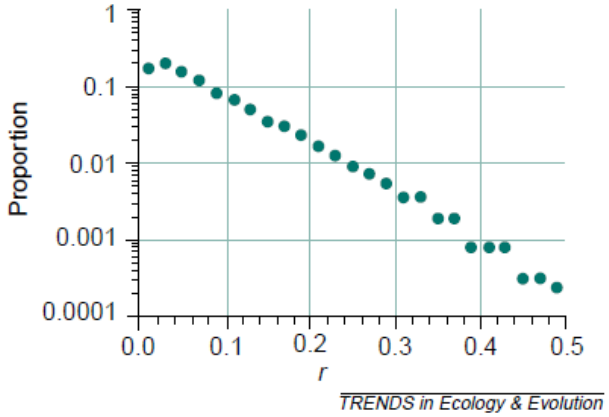


Fig. I. Distribution of phenotypic effects, *r*, among genes fixed during response to selection, where evolution occurred in Fisher's geometric model. The distribution is approximately exponential (a straight line on a semi-log plot). The simulation results shown reflect many realizations of adaptive walks to the optimum in a 25-dimensional (character) phenotypic space. Response to selection involved fixation of new mutations. For details, see Refs c,e.

{Fig. 9.qq = use the figure above from Orr 2001 to back calculate the distribution before log transforms; will need to explain the r scale in the caption; call it something else on the fig itself since r – the symbol - is used in so many other chapters for other things}

9.7 The analysis of divergent lines produced by deliberate selection, QTL analysis

Since the earliest days of genetics, crosses between lines that have diverged in phenotype have been used to diagnose the genetic basis of particular traits (Nilsson-Ehle 1909, East 1916). Modeling is simple if two parental lines, P_1 and P_2, are inbred as well as divergent. In that case, we can easily show that variation in the first generation hybrids (F_1) is wholly environmental, just as it is in the two parental lines. Second generation hybrids, produced by choosing F_1s at random and crossing them to produce the F_2, are a different matter. Variation in the F_2 exceeds that in the F_1 and parentals due to genetic segregation (Fig. 9.qq), and likewise in backcrosses produced by crossing the F_1 with P_1 or P_2. This blooming of genetic varation in second generation hybrids has made them popular with geneticists for more than 100 years, but that popularity does not mean that genetic variation in F_2 and backcross generations is typical of standing variation in natural populations. Usually the parental lines have been driven apart by natural or deliberate selection, so that the genes we detect in F_2 and backcrosses are ones that have responded to directional selection and have been pushed to or near fixation. The loci involved in divergence may or may not be responsible for genetic variation within natural populations.

Steady improvement in the analysis of second generation hybirds has been made since 1908. Early tests for polygeny were based on comparison of variance between first and second generation hybrids and were plagued with many assumptions, some of which can be relaxed (Castle 1921, Wright 1968, Lande 1981). Later analyses used chromosome markers to associate phenotypic differences with particular linkage groups (Sax 1923). Analyses of this kind have advanced to finer and finer scale mapping and the use of maximum likelihood (ML) for statistical inference. Genomic regions that are statistically associated with phenotypic differences in second (or later) generation hybrids are called *quantitative trait loci* (QTLs).

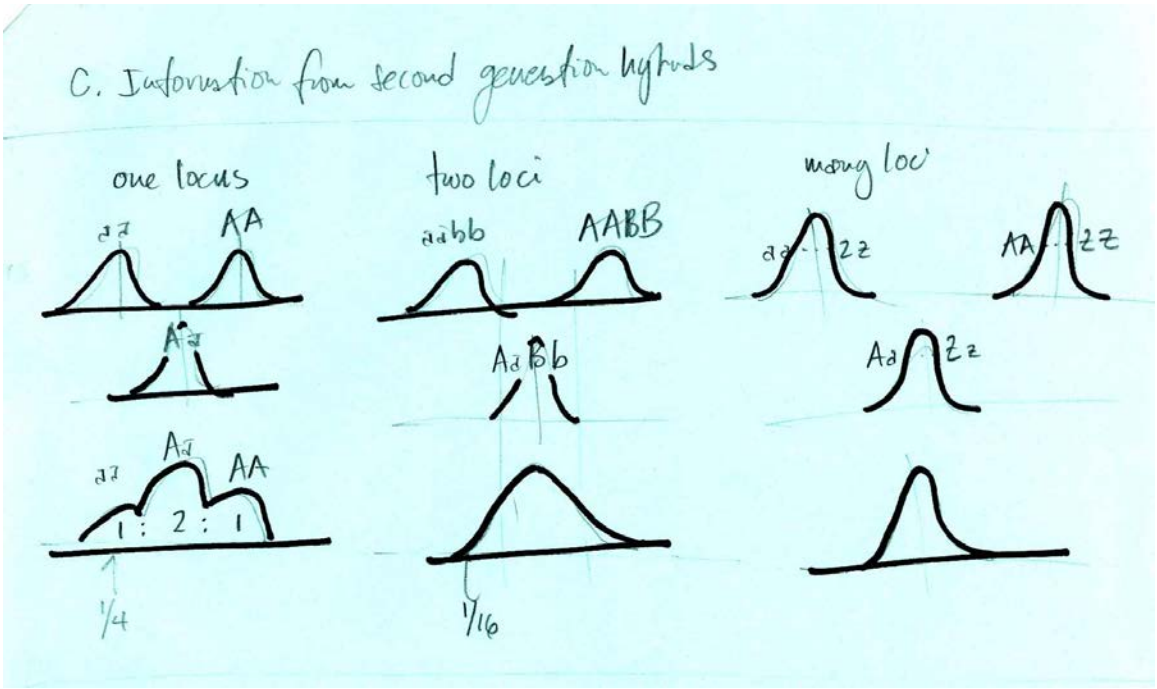


Figure 9.qq. Expansion of trait variance in the F_2 can be used to diagnose polygeny. If parental lines, P_1 and P_2, are inbred, all variation in that generation and in their hybrids (F_1) is environmental. The expansion of variance going from the F_1 to the F_2 is a consequence of genetic segregation and can be used to diagnose polygeny. Consider three models with additive genetic effects that differ only in number of

loci. (a) With one locus, variance in the F_2 is maximal. (b) With two loci, expansion of variance in the F_2 is much less. (c) With 24 loci, variance expansion is barely detectable {use Wright's formula to determine var in F2 and re-draw this figure; the last row can be drawn as a compounds of 3=2*2-1, 4*4-x and 24*24-y normal distributions, with their total vars matching Wright's formula}.

ML methods make use of correlations between phenotypic trait score and genomic markers in backcross, F_2 or derived progenies. These correlations are in turn produced by the linkage disequilibrium generated by mixing the P_1 and P_2 genomes. The trick is to use ML to estimate the position of the QTLs. Using Lander & Botstein's (1989) likelihood model, we wish to evaluate the evidence for a QTL at a particular marker position in the genome. We will use a backcross progeny obtained by crossing the F_1 with one of the parental populations, P_1. Our model for the phenotypic score of the *ith* individual in that backcross progeny is

$$z_i = a + bg_i + \varepsilon, \qquad \text{(xx)}$$

where g_i is an indicator variable that denotes the number of alleles from P_2 (0 or 1) at our marker locus, and ε is a normally-distributed error contribution with a mean of 0 and variance σ^2. b is an unknown parameter that represents the phenotypic effect of a single allele substitution at a putative QTL. To use the ML approach, we need an expression for a probability in terms of the unknown parameters. We have already made an assumption about the distribution of residuals, ε. To proceed we need to rearrange (xx) so that we have an expression for ε in terms of z_i, a, b, and σ^2. We now wish to estimate a, b and σ^2 by maximum likelihood. In other words, we wish to find the values of these parameters that maximize the probability $L(a, b, \sigma^2)$ that the observed data would have occurred. Given our model (xx) for a regression with normally distributed residuals,

$$L(a, b, \sigma^2) = \Pi_i \, p((z_i - (a + bg_i)), \sigma^2),$$

where $p(x, \sigma^2)$ is the probability density for the normal distribution of ε with mean 0 and variance σ^2. Notice that to do this calculation for a set of individuals in the backcross progeny, we need to know only each individual's phenotype (z_i) and the number of P_2 alleles it carries at the marker locus (i.e., g_i). We call the likelihood that maximizes this function $L(\hat{a},\hat{b},\hat{\sigma}^2)$, where $\hat{a},\hat{b},\hat{\sigma}^2$ are the values of the parameters that give this maximum value (i.e., the unconstrained maximum likelihood estimates).

We can use a likelihood ratio to access the evidence for a QTL. The constrained maximum likelihood estimates under the assumption that $b=0$ are $(\bar{z}_1,0,\sigma^2_{B1})$, where $\bar{z}_1$ is the mean phenotype in P_1 and σ^2_{B1} is the variance of the backcross population (i.e., the cross between P_1 and F_1). This set of parameters can be used to compute a value for the likelihood, $L(\bar{z}_1,0,\sigma^2_{B1})$, that is constrained in the sense that the markers have no effect on the phenotype z_1. The evidence for a QTL is then given by the so-called LOD score, the log of the ratio of the unconstrained and constrained likelihoods,

$$LOD = \log_{10}[L(\hat{a},\hat{b},\hat{\sigma}^2) / L(\bar{z}_1,0,\sigma^2_{B1})], \qquad \text{()}$$

which indicates how much more probable the data are when one assumes that a QTL is present versus assuming that one is absent … Fig. 9.5 = graph of LOD as a function of genomic position …. *LOD* (times a constant) is χ^2-distributed with 1 d.f.

9.8 QTL analysis of floral morphology and coloration in *Penstemon* {need something simpler since this example is so multivariate!} … Fig. 9.6 = composite showing results.

9.9 **Summary of QTL results** …
{need to distinguish in the examples that follow in evidence drawn from inbreeding of a single pop and evidence derived by crossing two divergent lines or species; want to use only the 2nd type of data; bristle numbers below may represent the 1st type}

see reviews by MacKay 2001a, 2001b; 2004; etc {see also Erickson et al 2004; Abiola et al 2003, Doerga 2003, Kearsey & Farquhar 1998; read Barton & Keightley 2002}

… results biased towards detecting loci of large effect and not detecting loci of small effect (*see discussion on p. 139 of Kearsey & Farquhar 1998; Goring et al 2001*)

… present summary with figures and tables

Table 9.qq (from Mackay 2001a)

Table 1 | **Variation for quantitative traits is due to multiple loci**

Trait*	Chromosome(s)‡	Number of QTL	References
Sternopleural bristle number	3	17	13
Sternopleural bristle number	1,2,3	22	19,21
Abdominal bristle number	1,2,3	26	19,21
Longevity	1,2,3	19	23–25
Wing shape	3	11	22
Competitive fitness§	1,2,3	6	29
Reproductive success§	1,2,3	2	28
Morphology of male genital arch	1,2,3	19	27

*Most studies mapped quantitative trait loci (QTL) affecting variation within *D. melanogaster*. The exception was the study of QTL affecting variation in morphology of the posterior lobe of the male genital arch between *D. simulans* and *D. mauritiana*. ‡*Drosophila* has three major chromosomes; the tiny fourth chromosome represents approximately 1% of the genome and does not recombine. §The low number of QTL for these fitness traits is probably a consequence of the reduced power to detect QTL for traits with high environmental variance.

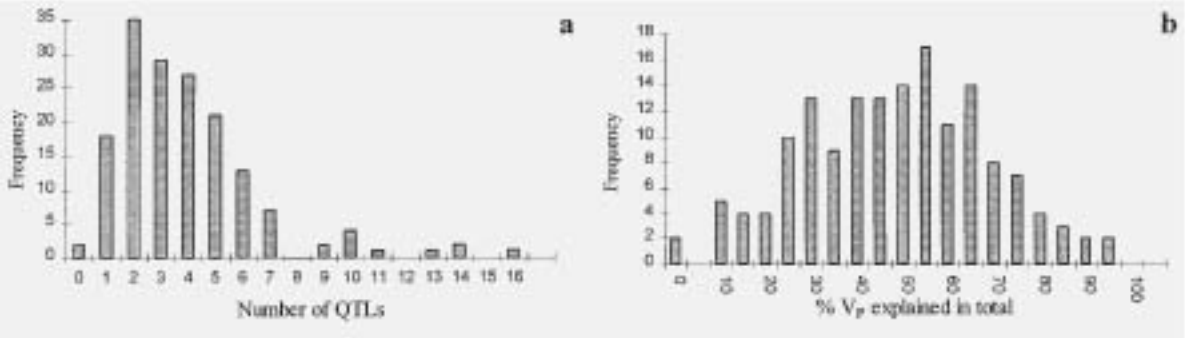


Figure 9.zz. Summary of the results of QTL analysis of 176 trait-environment combinations in in crop plants and *Arabidopsis*. (a) Histogram of the number of QTLs reported. (b) Histogram of the proportion of phenotypic variance explained (from Kearsey & Farquhar 1998)

Kearsey & Farquhar (1998) summarized the results of QTL analysis in 47 plant studies, representing 176 trait-environment combinations. Although the mean number of QTLs reported is about 4 and the mode is 2, the distribution is skewed to the right, with a few studies reporting more than 12 (Fig. 9.zza). The authors point out that the results are undoubtedly biased towards loci of large effect and that at the time of the summary it was technically difficult to detect more than 12 loci. The proportion of phenotypic variation in the analyzed (hyper-segregating) population averaged about 46%, but the proportion varied hugely among studies (Fig. 9.zzb).

QTLs for particular traits are usually scattered throughout the genome rather clumped in one region. This scattered pattern is conspicuous for QTLs that affect growth in house mice (*Mus musculus*) (Figure 9.zx).

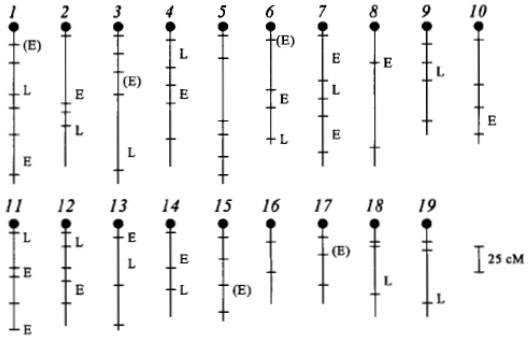


FIGURE 2.—Relative positions of QTLs affecting early (E) and late (L) growth. Parenthetical entries represent locations with exclusive effects on early or late weights but not on growth itself.

Figure 9.zx. Genomic positions on 19 linkage groups of 75 QTLs that affect growth in mice. E and L denote effects on early and late growth respectively. Entries in parentheses affect early or late weight but not growth itself. (from Cheverud et al. 1996)

9.3 The analysis of divergent lines produced by deliberate selection, tests for deviation from additive inheritance

Deviations in the positions of the mean in F_1 and second generation hybrids from additive expectations can provide evidence for dominance, maternal effects, and sex-linkage, depending on the nature of the deviations (Wright 1968 &/or 1977 – check). For example, deviation of the means of both sexes in the F_1 towards one of the parentals indicates *directional dominance*. That is to say, one or more underlying factors shows dominance in effects on the trait, causing an overall shift in the mean away from intermediacy. Consider the case of characid fishes of the *Astyanax* complex that exist in both surface- and cave-dwelling populations in Mexico. The inheritance of eye size has been studied by crossing these two ecotypes (Wilkins 1970, 1971) ...

the F_1 mean deviates towards the eyed parental mean (Fig. 9.cc), indicating directional domiance for the presence of eyes ... the failure of the F_2 sample to encompass the positions of the parental means suggests that several factors may be responsible for ecotypic differentiation in eye size.

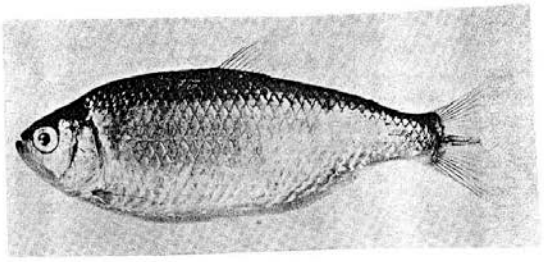


Abb. 1. Astyanax mexicanus, ♀

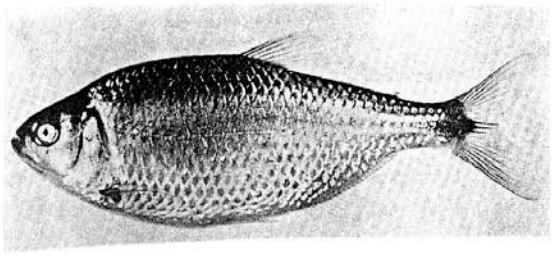


Abb. 3. F1-Generation *Astyanax* x *Anoptichthys*, ♀

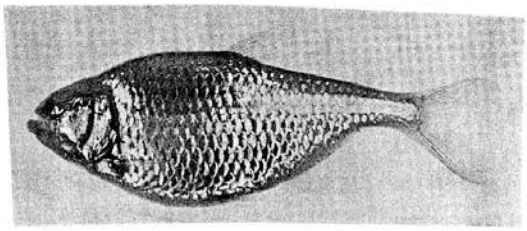


Abb. 2. Anoptichthys antrobius, ♀

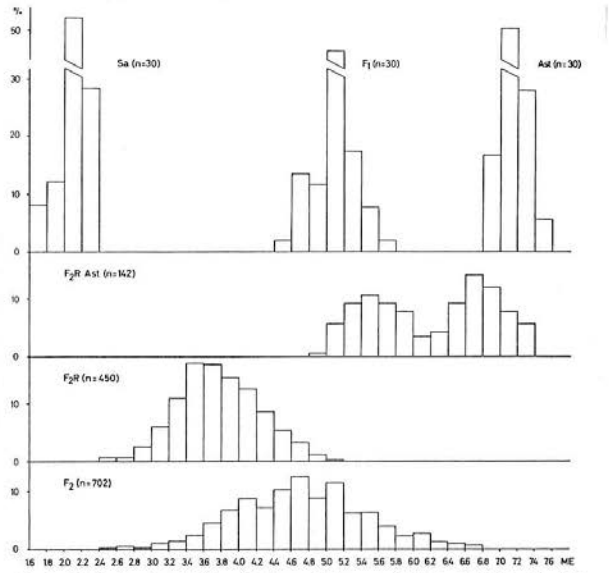


FIG. 6. Distribution of eye-ball sizes of epigean and hypogean *Astyanax* populations and their crossings (Sa = hypogean population, Ast = epigean population, F_1R = backcross with a hypogean population, F_2R Ast = backcross with the epigean population, ME = units of measurement).

Wilkens 1970, 1971

A simple visual test for the adequacy of the additive model of inheritance can be conducted by plotting the variances of the parental, F_1, and second generation hybrids as a function of their means. The prediction from the additive model is that resulting graph will form a triangle (Fig. 9.rr, Lande 1981b). A sample of six traits analyzed with this technique shows reasonably good fits to the additive model, within the limits of sampling, but there are some exceptions (Fig. 9.ss, Lande 1981b). Eye diameter in *Astyanax*, for example, shows discrepancies in the backcross variances, perhaps due to the segregation of a gene with major effect in one of the backcrosses. In the case of human skin color, the fit is so poor that the causes are hard to diagnose.

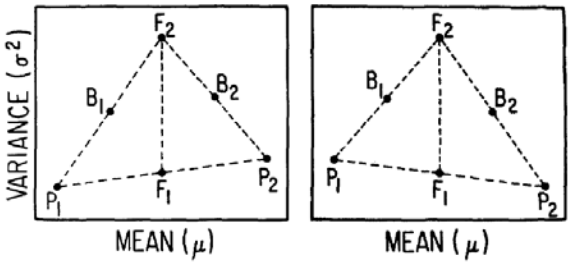


FIGURE 1.—Theoretical means and variances of a quantitative character in parental and hybrid populations. On a transformed scale of measurement, the mean phenotypes are additive. Graphing the variances against the means gives a triangular pattern, with F_1 and backcross populations at the midpoints of the edges connecting the parental and F_2 populations.

As a general rule … {summary statement here drawn from Lande or Wright summarizing the accumulated literature with respect to the adequacy of the additive model}

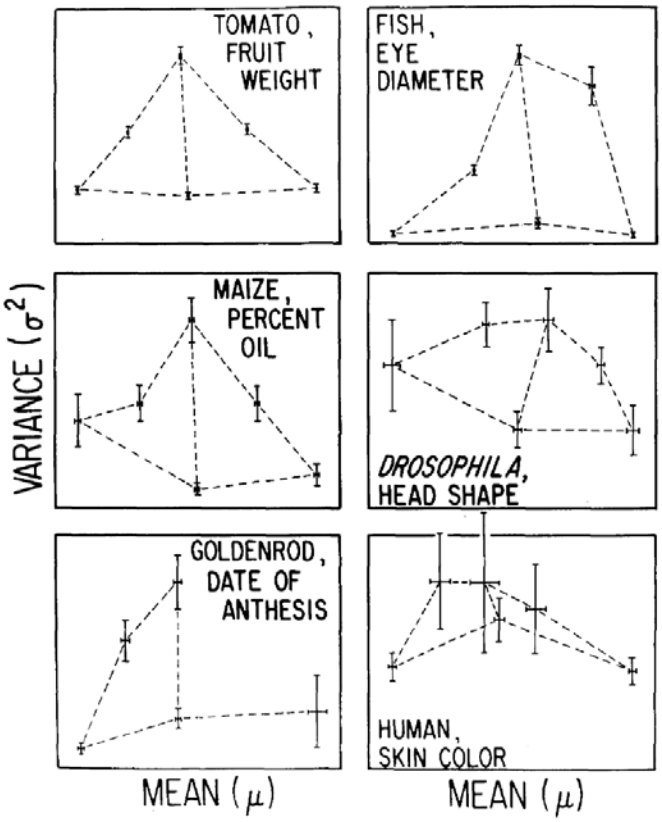


FIGURE 2.—Transformed phenotypic means and variances plotted with standard errors, from the data on crosses summarized in Table 3.

9.10 Molecular basis of responses to selection

David Stern and his colleagues have provided a particularly detailed analysis of the polygenic changes that underlie the evolution of bristle patterns in *Drosophila*. This case study is of special interest because it also tests the proposition that change in the same genetic elements occurs in separate lineages during parallel evolution in a particular trait. The cuticles of larval *Drosophila* are usually covered with numerous small bristles (trichomes), but these bristles have been lost in a few lineages, for example in *D. sechellia*. Stern and his colleagues assayed the genetic changes responsible for the morphological difference between *D. sechellia* and *D. melanogaster* that accumulated over a 500,000 year period. Those assays revealed changes in five cis-regulatory regions of the ca. 110 kb svb gene (*shavenbaby*) that encode a transcription factor which orchestrates trichome morphogenesis. Analysis of the changes at one of these ca. 5 kb transcriptional enhancers revealed 14 single-nucleotide changes, each of which had a small effect in reducing trichome number (Frankel et al 2011). Taken together these substitutions accounted for the melanogaster-sechellia difference in trichome number, but the changes were not simply additive and involved substantial instances of epistasis. Rate tests based on DNA sequence analysis confirm our suspicions that the molecular differentiation was driven by positive selection (Frankel et al. 2011), which at the morphological level presumably coincided with some change in larval ecology. Changes in these same regulatory elements are responsible of the independent loss of trichomes in the *Drosophila virilis* group (Sucrena et al. 2003). This case study, by virtue of its detailed molecular dissections, provides a powerful example of the rule that morphological evolution proceeds by many small steps at the molecular level, rather than by single jumps.

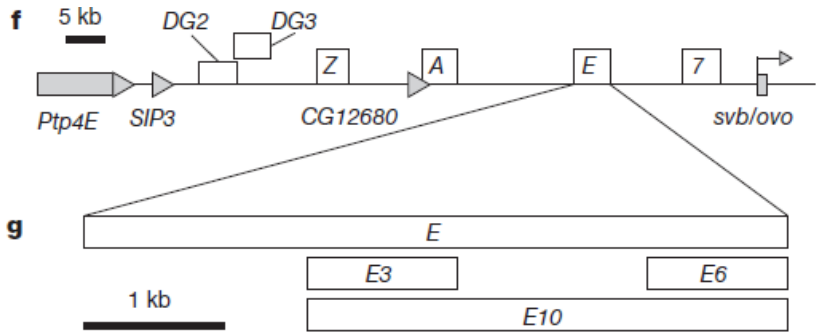


Figure 1 | The pattern of trichomes has evolved between *Drosophila* species owing to changes in the enhancers of the *svb* gene. a, Lateral view drawing of *D. melanogaster* (**d**) and *D. sechellia* (**e**). f, Diagram illustrating the location of the six enhancers of *svb* (open boxes). The enhancers *7*, *E* and *A* were referred to as *proximal*, *medial* and *distal*, respectively, in ref. 25. Genes in the region are indicated with grey boxes and only the first exon of *svb* is shown. g, Summary of the dissection of the *E* enhancer in *D. melanogaster*. Boxes indicate the enhancer constructs discussed in the text. h, The *E3* region drives expression in