Rates of change of genetic parameters of body weight in selected mouse lines

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Summary

A method based on the animal model is described which allows the estimation of continuous changes in variance components over time using restricted maximum likelihood (REML). The method was applied to the analysis of a selection experiment in which a foundation population formed from a cross between two inbred strains of mice (C57BL/6J and DBA/2J) was divergently selected for 6 week body weight over 20 generations. The analysis suggested that there was an increase in phenotypic variance of about 50% in the low selected lines over the course of the experiment which was attributed to increases in the environmental and additive variance components. Variance changes in the High selected lines were generally smaller than in the Low lines, although there was an estimated 20% increase in the environmental variance. Simple models to explain these effects involving dominance, linkage and epistasis were explored. Testing which of these was responsible for the variance changes noted in this experiment (if any) is difficult, although the epistasis and dominance models require less stringent conditions than the linkage model, and the dominance model is supported by evidence of heterosis in the F_1.

1. Introduction

An understanding of the nature of the genes influencing quantitative traits is of great importance for predicting the response to selection. The standard genetic model for quantitative traits is the infinitesimal model in which a trait is assumed to be influenced by many unlinked additive genes of small effect. Deviations from the predictions of the infinitesimal model indicate a failure of the model and can help in understanding the underlying genetics of the trait and in the development of more realistic models. Artificial selection experiments can provide opportunities to test the infinitesimal model by checking whether the observed selection response and changes in variance agree with predictions from quantitative genetic theory (Sheridan, 1988; James, 1990; Hill & Caballero, 1992). Estimation of changes in genetic parameters under selection have been made in several studies by splitting the data up into blocks of generations and analysing each block separately (e.g. Rahnefeld *et al.* 1963; Meyer & Hill, 1991; Beniwal *et al.* 1992). The simplest way to do this is to consider the generation

blocks as completely separate datasets and estimate variances for each block (Rahnefeld *et al.* 1963). This does not, however, take into account the effects of inbreeding and selection on the later generation blocks. This can be achieved by analysing the data with an animal model and including the pedigree back to the base population (Meyer & Hill, 1991). A more sophisticated analysis was performed by Beniwal *et al.* (1992) where the variance in separate blocks of generations was estimated simultaneously.

In the present paper, a method is described in which variances are allowed to change continuously over time by, in effect, fitting a linear regression on generation to all variance components. The method allows nesting of the regression within lines so changes in variance can be estimated separately for High and Low selection lines. This is important because in many cases where the infinitesimal model does not hold (i.e. if there was non-additive genetic variance present), the size and direction of any changes in variance would be affected by the direction and strength of selection and so could differ between the selection lines.

Data from a selection experiment on mice were analysed using this method. Changes of variance were estimated and compared against the predictions from

the infinitesimal model and the observed variance changes then used to make inferences about the effects of the genes controlling the trait.

2. Materials and methods

(i) *Selection lines*

The selection lines (the X-lines) were set up from a cross between two inbred mouse strains, C57BL/6J and DBA/2J, which were obtained from the Jackson Laboratory, Maine, USA in 1985 (see Keightley & Bulfield (1993) for more details). From the F_2 of this cross, lines were divergently selected for 6 week body weight for 20 generations with six lines being selected upwards, six downwards, and with one unselected control line. In total there were 6503 animals in the Low lines, 8401 in the High lines and 1208 in the Control line. Selection was on a within-family basis with each line being maintained with eight breeding pairs. The mating schedule was the same as that used by Falconer (1973).

(ii) *Realized heritability estimates*

Estimates of realized within-family heritability were calculated from the regression of cumulative selection on response using the divergence between pairs of Low and High selected lines. A pooled estimate was obtained using the means of all replicate lines. Standard errors were estimated assuming independence of the errors of the observations. This leads to an underestimate of the true standard error since the errors for subsequent generations are correlated (Hill, 1972). A mean estimate and empirical standard error were also calculated from the separate regression coefficients from each pair of replicates. The selection differentials were calculated from the mean within-sex within-litter deviations.

(iii) *REML analysis assuming homogenous variances*

Further analysis was undertaken using programs based on the derivative-free REML packages of Meyer (1988, 1989). An animal model was fitted to the data with generation, sex nested within line and generation, parity and litter size as fixed effects, and litter as an additional random effect uncorrelated with the main random effect. Sex was fitted as a nested effect because a significant change in sexual dimorphism was noted in the low lines over the course of the experiment. The model was

$$y = X\alpha + Z\beta + W\lambda + e,$$

where y is the vector of observations, α is the vector of fixed effects, β is the vector of additive genetic values, λ is the vector of litter effects, and e is the vector of environmental effects; α, λ, and e have mean zero and are uncorrelated. $\mathrm{Var}(\beta) = A\sigma_a^2$ where A is the

numerator relationship matrix and σ_a^2 is the initial additive genetic variance, $\mathrm{Var}(\lambda) = I\sigma_c^2$ where I is the identity matrix and σ_c^2 is the litter variance, and $\mathrm{Var}(e) = I\sigma_e^2$ where σ_e^2 is the environmental variance. X, Z, and W are incidence matrices. Phenotypic variance = $\sigma_p^2 = \sigma_a^2 + \sigma_c^2 + \sigma_e^2$, so the heritability = $h^2 = \sigma_a^2/\sigma_p^2$, and the litter or 'c-squared' coefficient = $c^2 = \sigma_c^2/\sigma_p^2$. All REML analyses used $\log_e$ transformed data to account for changes in variance due to differences in means between Low and High selected lines. Standard errors of variance components were estimated using the second derivatives of a polynomial approximation to the likelihood function.

(iv) *REML analysis allowing heterogenous variances*

Subsequent analyses used an extension to the animal model allowing (*a*) the fitting of separate variance components to blocks of animals and (*b*) variance components to change continuously over the course of the experiment (in effect fitting the variances as regressions on generation). In this case the blocks refer to the different selection directions, i.e. variance components were fitted separately to High and Low selected lines.

Part (*a*) was described by Beniwal *et al.* (1992). The (co)variance matrices for the random effects were split into contributions from the different blocks. For example, let V be the covariance matrix for a random effect so the Cholesky decomposition of V can be written as $V = TDT'$ where D is diagonal and T is lower triangular. Each element of D then corresponds to a level of the random effect, so D can be partitioned into a set of submatrices according to which block each random effect level is in. If there were n blocks then V can be written as follows:

$$V = T \begin{pmatrix} D_1 & 0 & \cdots & 0 \\ 0 & D_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & \cdots & D_n \end{pmatrix} T'.$$

Then if W_i is an incidence matrix such that the element $w_{jj} = 1$ if random effect level j is in block i and 0 otherwise and $\sigma_{v_i}^2$ is the variance component for the ith element:

Variance of random effect

$$= \sum_{i=1}^{n} T(W_i D) T' \sigma_{v_i}^2 = \sum_{i=1}^{n} V_i \sigma_{v_i}^2.$$

Part (*b*) was implemented by splitting the covariance matrices for the random effects into two such that, for example, $V = V_0 + bV_1$ for a linear regression. In this case, V_0 is equal to the normal covariance matrix and V_1 is equal to $TDRT'$ where $V = TDT'$ as before and R is a diagonal matrix with the ith element equal to $1/r_i$, r_i being the regression variable (generation in this case) for animal i.

Parts (a) and (b) can easily be combined so that the variance component regressions are nested within blocks. In the analysis described here a common 'intercept' variance was fitted to all lines with separate 'gradient' variances being fitted to the High and Low lines. The additive, common environment, and environmental variances, were all treated in this way. Standard errors for all variance components were estimated using quadratic approximations to the individual profile likelihoods (Meyer & Hill, 1992).

A simulation test of the above method was performed by analysing simulated data using (a) a large number (16 384) of unlinked genes of equal effect (i.e. as an approximation to the infinitesimal model) and (b) a smaller number of genes (32). In both cases the initial gene frequency was set to 0·5. The simulated data structure closely followed the real experiment except that a litter effect was not simulated or estimated to reduce the computing costs. The base population for the simulation was an F_2 formed from a cross between two inbred strains. The F_2 was then split into 12 selection lines, six of which were selected upwards and six selected downwards for 20 generations. Within each line there were eight full-sib families/generation and eight individuals/family. The best two individuals from each family were selected. For all the simulations, the additive variance (σ_a^2) was set to 1·0 and the environmental variance (σ_e^2) was set to 3·0 (these being close to the actual values derived from the data). For both cases (a) and (b) the simulation tests were replicated 10 times and the mean and empirical standard error of the replicate tests were calculated.

3. Results

(i) Responses

The selection responses in 6 week weight are shown in Fig. 1. There is a strong indication of directional dominance as the F_1 have a mean weight above the
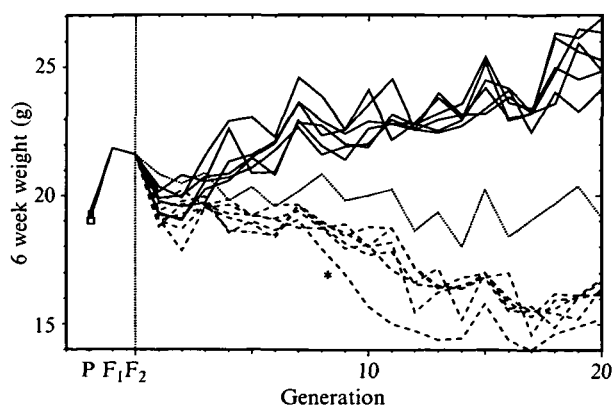

Fig. 1. Mean 6-week weights (g) averaged over sex of the 13 replicate lines (—, six High, – – –, six Low and ······, one Control). Subline B of the low lines (referred to in the text) is marked by a *. ■, DBA/2J; □, C57BL/6J.

Table 1. Linear regression of sexual dimorphism (male weight/female weight)* on generation fitted for High, Low and Control lines separately

Line	Regression coefficient	t-ratio†
High	−0·000787	−1·58
Low	−0·003370	−6·78‡
Control	−0·000009	−0·01

* Weights are the mean body weights for each sex averaged within line (High, Low & Control) and generation.
† t-values were non-significant at the 5% level.
‡ Significant at the 0·1% level.

average of the parental lines. The phenotypic standard deviation of 6 week body weight is ≈ 2 g so the total response is about two standard deviations in both directions.

Subline B of the low lines (marked * in Fig. 1) shows a markedly different response to the other lines, being at one point (around generation 10) about 1 s.d. lower than the other lines. Although the difference between subline B and the other lines reduced later on, at the end of the experiment there is still a clear difference between this subline and the others. It therefore seems probable that the effect is caused by a rare event which only occurred in that line such as a mutation or a rare recombination.

(ii) Sexual dimorphism

If males and females are considered separately, differences in the selection responses are seen. In the control lines, both sexes show a slight decrease in body weight over the course of the experiment (a further indication of directional dominance). In the selected lines, the males show a roughly equal response in both directions, but the females show significantly less response to downwards selection. The two sexes were therefore converging since the males weighed more than the females. This effect was still apparent when using log transformed data. Sexual dimorphism (measured as the ratio of male to female weights), therefore, decreased over the course of the experiment in the Low selected lines as shown by the regression of male/female weight on generation (Table 1).

A similar, although less strong, effect was reported by MacArthur (1944) from a selection experiment on mice where in low selected lines the response in females was proportionally less than that in males. A possible explanation for this effect is that fertility in females may depend more strongly on body weight than it does in males due to generally higher physiological costs of reproduction in females. This could cause the females to respond less strongly to downwards selection than males if, for example, the smallest females were unable* to produce offspring.

Table 2. *Realized heritabilities calculated from the regression of response against cumulated selection differentials for the divergence between pairs of lines*

Rep. pair	b	S.E.
A	0·191	0·016
B	0·215	0·021
C	0·201	0·018
D	0·230	0·014
E	0·219	0·017
F	0·242	0·014
Pooled	0·220	0·0074
Mean†	0·216†	0·0077†

b, Regression coefficient. S.E. = standard error of regression except where marked †.
† Arithmetic mean of regression coefficients among replicates with empirical standard error.

(iii) Realized heritabilities

Realized within-family heritabilities (Table 2) give a mean estimate from all replicates of 0·2 with an empirical standard error of 0·008. The pooled estimate (achieved by analysing all replicates together) was again 0·2 with the standard error of the regression being 0·007. This is slightly lower than the standard error of the mean estimate, but underestimates the standard error of the heritability estimate since it assumes independence of the residuals (Hill, 1972).

(iv) REML analysis assuming homogenous variances

The homogenous variance REML analysis was conducted for all lines together (Table 3 a). The heritability estimate is larger than the mean realized estimate and the standard error is slightly higher (0·012 compared to 0·008). The more complex model used for the REML analysis may account for the lower precision of the heritability estimate. The two heritability estimates are not of the same quantity since the realized heritability is an estimate of within-family heritability (h_w^2) whilst the REML estimate is of the individual heritability (h^2). To compare the estimates the REML heritability estimate must be converted into the within-family estimate using the following formula (Falconer, 1989):

$$h^2 = h_w^2(1 - t)/(1 - r),$$

where r = the relationship between family members (1/2 in this case) and t = the intra-class correlation of family members = $\frac{1}{2}h^2 + c^2$. As $t \approx 0.5$ using the estimates obtained from the analysis, h^2 and h_w^2 are almost identical.

(v) REML analysis allowing heterogenous variances
(a) Simulated data

The means and empirical standard errors from 10 replicates of the simulation analysis using (a) 16384

Table 3. *REML estimates of variance components and genetic parameters using log transformed data fitting (a) constant variance components, (b) linear regressions to all variance components nested within lines and (c) as previous analysis but omitting subline B of the Low line*

	Var. Components × 10⁻³					
	$\hat{\sigma}_a^2$ (S.E.)	$\hat{\sigma}_c^2$ (S.E.)	$\hat{\sigma}_e^2$ (S.E.)	$\hat{h}^2$ (S.E.)	$\hat{c}^2$ (S.E.)	$\hat{e}^2$ (S.E.)
(a) Homogenous variance analysis						
	3·31	4·38	4·49	0·27	0·36	0·37
	(0·15)	(0·18)	—	(0·01)	(0·01)	—
(b) Heterogenous variance analysis – all lines						
Initial values	2·69	4·55	3·33	0·25	0·43	0·32
	(0·26)	(0·13)	—	(0·02)	(0·00)	—
Low line increments*	2·66	−1·26	4·53	0·07	−0·23	0·16
	(1·15)	(0·72)	(0·53)	(0·07)	(0·04)	(0·05)
High line increments	0·96	−0·26	0·76	0·05	−0·07	0·02
	(0·84)	(0·72)	(0·37)	(0·06)	(0·04)	(0·04)
(c) Heterogenous variance analysis – omitting Low subline B						
Initial values	2·49	4·65	3·53	0·23	0·44	0·33
Low increments*	1·01	−1·08	3·98	0·01	−0·19	0·18
High increments	1·94	−0·48	0·20	0·13	−0·10	−0·03

* Increments are the estimated differences between components at the start and end of the experiment. Variances are assumed to change linearly between their starting and finishing values.

Table 4. *REML estimates of the additive and environmental variance components from simulated data using (a) 16384 additive genes and (b) 32 additive genes fitting linear regressions to both variance components nested within lines. The results given are the mean of ten replicates along with the empirical standard errors*

		Initial values		Low line increments		High line increments	
		$\hat{\sigma}_a^2$ (s.e.)	$\hat{\sigma}_e^2$ (s.e.)	$\hat{\sigma}_a^2$ (s.e.)	$\hat{\sigma}_e^2$ (s.e.)	$\hat{\sigma}_a^2$ (s.e.)	$\hat{\sigma}_e^2$ (s.e.)
(a)		1·02 (0·02)	2·96 (0·02)	0·00 (0·04)	0·04 (0·03)	0·01 (0·04)	0·02 (0·05)
(b)		1·01 (0·03)	3·02 (0·02)	−0·27 (0·05)	−0·04 (0·04)	−0·23 (0·07)	0·02 (0·04)

The simulated values for the components are $\sigma_a^2 = 1\cdot00$ and $\sigma_e^2 = 3\cdot00$. σ_e^2 should not change over time but σ_a^2 should show a decrease when only a few genes are simulated due to changes in gene frequency. Note that changes in σ_a^2 due to inbreeding and selection are accounted for by inclusion of the A matrix into REML.

genes and (b) 32 genes are given in Table 4. For both cases the estimated initial values for the variance components were close to the simulated values and the changes in σ_e^2 were not significantly different from zero. There is a difference between the two cases, however, with regard to the change in σ_a^2 which was not significantly different from zero for case (a) but was significantly less than zero for case (b), indicating a reduction in σ_a^2 greater than would be predicted under the infinitesimal model. This is to be expected with only a small number of genes affecting the trait because there will be changes in gene frequencies away from 0·5 under selection.

Experimental data

The results from the analysis of the experimental data fitting linear regression coefficients to all variance components (additive, common environmental and environmental) nested within the High and Low lines are shown in Table 3b. The standard errors presented are calculated using a quadratic approximation to the profile likelihood for each component. The main changes are found in the Low lines where there is a substantial change in all variance components over the course of the experiment. The phenotypic variance in the Low lines increases from $10\cdot6 \times 10^{-3}$ to $16\cdot5 \times 10^{-3}$; this increase is a result of increases in both the additive and environmental variance with the litter variance, by contrast, decreasing. When the variances are considered as proportions of the total variance at the beginning and end of the experiment, h^2 increases from 0·25 to 0·32 while c^2 decreases from 0·43 to 0·20. These results indicate that the response to selection in the Low lines should increase over time due to the increases in h^2 and σ_p^2, and the observed response (Fig. 1) does support this, with the Low lines showing

an acceleration of response over the middle section of the experiment.

The analysis was repeated omitting subline B of the Low lines (which showed a very different response from the other sublines; Table 3c). The Low lines show a smaller increase in σ_a^2 than in the previous analysis while the High lines show a larger increase, although the differences between the analyses are not significant.

4. Discussion

A significant increase in additive and environmental variance under selection was detected in the low selected lines, a result contrary to the predictions of the infinitesimal model. There are several possible causes for this increase. It has been noted before that inbreeding can result in a reduction in the capacity of organisms to regulate developmental processes. This can lead to inbred lines being more variable than the outbred parental lines (Maynard Smith, 1989). Most of the increase in variance was 'attributed' to an increase in environmental variance. This does not, however, necessarily mean that the increase is mainly non-*genetic* but rather that it is non-*additive* genetic in nature. Genetic variance changes that do not fit the model of a linearly increasing additive variance may be erroneously partitioned into the environmental or litter components. Increases in genetic variance could be caused by new mutations, non-additive gene action (i.e. dominance or epistasis) and the breakdown of linkage disequilibrium. These possibilities are discussed below.

Increases in additive genetic variance have been reported in small populations undergoing random drift where the infinitesimal model would predict a decrease (Bryant & Combs, 1986). A relevant example

of this is a study (Rahnefeld *et al.* 1963) of a selection experiment in mice using a cross between two unspecified inbred lines as the foundation population. When the additive variance in individual generations was estimated using the average value obtained from the sire component and parent–offspring regressions they found a slight (but non-significant) increase over the course of the experiment.

The analysis presented here shows that the infinitesimal model cannot adequately explain the results of the X-Line experiment. One possible alternative model would be a trait which is controlled by a relatively few genes. Simply reducing the number of genes in the model, however, leads to a poorer fit since if gene action is assumed to be exclusively additive then such a model predicts that the additive variance should decrease under selection due to changes in gene frequency away from 0·5. This is shown by the simulations using 32 genes described earlier. Several studies have reported decreases in additive variance under selection (Meyer & Hill, 1991; Beniwal *et al.* 1992), which is more in line with what would be expected if the trait was largely under the control of a few additive genes.

If there was some directional dominance in gene action, as indicated by the hybrid vigour shown in the F_1 generation, then this could lead to an increase in variance under selection because the maximum genetic variance is no longer when the gene frequency is at 0·5. Under this model, however, whilst selection in one direction would produce a rise in genetic variance, selection in the opposite direction would yield a decrease in variance faster than that under a purely additive model, a pattern of variance changes not seen in this study.

Interaction between rather than within loci can also increase additive variance as frequencies shift from 0·5. If a population experiences a bottleneck and is then maintained with a small population size so that gene frequencies alter under drift, the additive variance can increase substantially for many generations (Goodnight, 1988). This can be explained by an epistatic model of gene action since epistatic variance is at a maximum at intermediate gene frequencies. As genes become fixed by drift or selection, the epistatic variance is converted into additive variance. If this is enough to compensate for the loss of initial additive variance caused by genes approaching extreme frequencies then the additive variance could increase under selection in both directions.

An increase in genetic variance can also be caused by a breakdown of linkage disequilibrium between pairs of loci of opposite effect. When the genes are totally associated, the variance resulting from the gene pair will be proportional to the square of the sum of the effects of the two genes (assuming additivity), whereas if the genes are not associated then the variance resulting from the pair will be proportional to the sum of the squares of the effects of the two genes. If the effects of the genes oppose each other then the variance resulting from the genes with total linkage disequilibrium will be less than that with no disequilibrium. Since the F_1 population is in total linkage disequilibrium, as the experiment proceeds this should break down, potentially leading to an increase in genetic variance. The size and duration of any increase are dependent on the degree of linkage; if the genes are tightly linked then a small, gradual increase will result and if the genes are loosely linked or unlinked then a large, but short-lived, increase will occur. The main problem with this model is that adjacent genes must be in repulsion (having opposing effects). For example, in the simulation described earlier with 16384 unlinked additive genes, the parental lines were set up with alleles assigned randomly to each parent. In this situation there was no change in additive variance apart from that predicted by the infinitesimal model, so it is not enough for ' + ' and ' − ' alleles to be assigned randomly, rather they must be arranged as ' + − + − + − + − ' etc. A possible mechanism for achieving this is stabilizing selection in the parental lines because if an allele becomes fixed at one locus then there will be a selection for a 'compensatory' allele at another locus to 'balance out' the effect of the first allele so that the overall effect of the chromosome is minimized (Mather, 1941; Lewontin, 1964). The genes either have to be tightly linked, however, or the selection very strong for the gene combinations to depart much from a random arrangement (Wright, 1969).

Rather than the increase in variance resulting from an unlocking of existing genetic variance through changes in gene frequency or loss of disequilibrium, mutation could lead to new genetic variance being generated. The anomalous response of subline B of the Low lines could be caused by a new mutation arising in this line during the experiment. Since mutations would enter the population at low frequencies, favourable mutations could cause an increase in genetic variance as their frequency moved towards 0·5, although this increase would be offset by losses caused by inbreeding. Current estimates of the amount of new genetic variation in body size of mice arising from new mutations are large enough to account for the increase in heritability seen in this study (Keightley & Hill, 1992; Hill *et al.* 1994).

In conclusion, it is clear that the infinitesimal model cannot adequately explain the results presented here. Phenotypic variance has increased significantly under selection in both directions, and several models are presented as possible candidates for this increase, although determining which is closest to the actual model is difficult. The directional dominance model does not predict the observed pattern of variance changes so is unlikely to be the main cause of the increase in variance. It is, however, likely to play a role since it is evident that some directional dominance

is present. The linkage model seems unlikely given the stringent conditions that must be met for it to produce the effect seen here. An epistatic model has a more plausible explanation for how it could occur. Epistatic variance will be highest at intermediate gene frequencies because it is caused by the interactions between loci, and as loci become fixed there is less chance of interactions. In the inbred founder lines there should be no genetic variance of any type; however, crossing the lines restores some of the epistatic variance present in the ancestral population from which the lines were originally derived. Drift then acts to convert this epistatic variance into additive variance as described earlier. Mutation could also be an important source of new genetic variation, although this should have resulted in much divergence between the replicate lines and, apart from subline B of the Low lines, this divergence is not apparent.

There is potential for further analysis that could shed light on the causes of the increase in variance seen here. The model of analysis could be extended explicitly to include non-additive and interaction terms into the estimation process. Also, marker frequencies measured at the end of the experiment could be used to obtain estimates of gene effects linked to the markers (Keightley & Bulfield, 1993) and interactions between genes, eventually producing a distribution of gene effects and interactions which may explain the variance increase.

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