ESTIMATION OF GENETIC PARAMETERS

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SUMMARY

This is a review of various aspects of estimation of genetic parameters, concentrating on developments since the last World Congress. Improvements in algorithms to estimate variance and covariance components are described. We discuss the relevance of these procedures, developed for unselected populations, when they are applied to selected populations and indicate unresolved difficulties. We comment on the use of mixed model methodology to estimate realised heritabilities. We consider the design of experiments to estimate multivariate parameters. In particular, we show that for bivariate uncorrelated data the variance of the estimated genetic parameters can be reduced by 0.4 relative to more conventional designs.

INTRODUCTION

Thompson (1982) reviewed methods of estimation of variance and covariance components. Part of our paper is related to updating that review and pointing out improvements in algorithms and their application to selected data.

Often the precision of estimates, especially from multivariate data, is low. We investigate the design of bivariate experiments showing that by suitable selection of parents we can increase the precision of estimates.

ALGORITHMS FOR VARIANCE COMPONENT ESTIMATION

For illustration we consider estimation in the linear model

$$y = Xa + Zb + e \qquad (1)$$

where y is a nx1 vector of observed responses, X and Z are known matrices of size nxp and nxq, a is a px1 vector of fixed effects, and b is a qx1 vector of random effects distributed as $N(0, \sigma^2_b I)$ and e is a vector of residual terms distributed as $N(0, \sigma^2 I)$. If the elements of X and Z are zero or one and each row of X and Z has only one non zero element then (1) can be thought of as a ANOVA mixed model.

For this model Patterson and Thompson (1971) introduced the idea of residual maximum likelihood (REML) using the likelihood (L) of error contrasts to estimate the variance components σ^2_b and σ^2. Iterative schemes are needed if the design is not balanced. Patterson and Thompson (1971) gave schemes based on expected values of second differentials of L. However the computation of second differentials can be complicated, for example Meyer (1983), and using first differentials of L might take more iterations but could be computationally cheaper.

One general scheme, possible whenever there is missing data, which can be thought of as using the first differentials is the expectation-maximisation (EM) algorithm (Dempster et al., 1977). In our case the missing data are the random effects b and e. The estimation of variance components using the EM algorithm has been described for model (1) by Dempster et al. (1984) and for other genetic models by Henderson (1985a,b). This has been despite indications (Thompson, 1979) that the procedure can be slow to converge, especially with animal breeding data.

For balanced designs, analyses of variance can be easily constructed and estimators for the various mean squares trivially constructed and then simply transformed to give efficient estimates of the variance components. This raises the question whether the EM algorithm can be improved by a transformation of parameters.

Thompson and Meyer (1986) have shown that such an improvement in the rate of convergence is possible. For example in model (1) with p=1 and a representing an overall mean effect and n/q observations involving each random effect (i.e. a balanced design) then a natural parameterisation is σ^2 and $\sigma^2_b + q\sigma^2/n$. An EM algorithm, for these parameters, converges in one iteration. Obviously in animal breeding studies data is not often balanced but the transformation from σ^2, σ^2_b to σ^2 and $\sigma^2_b + \sigma^2/k$, where k is an average number of observations on the random effects, can dramatically improve convergence. Note that as k tends to infinity we get the more usual EM algorithm.

The same argument can be applied to other designs, for example for an hierarchical analysis between sires, between dams within sires and within dams. Then the natural parameters are σ^2, $\sigma^2_d + \sigma^2/k_1$ and $\sigma^2_s + \sigma^2_d/k_2 + \sigma^2/k_1k_2$ where k_1 and k_1k_2 are measures of dam and sire family size (Thompson and Meyer, 1986). Sometimes σ^2, σ^2_d and σ^2_s can be interpreted as $\sigma^2_p - \sigma^2_A/2-3\sigma^2_D/4$, $\sigma^2_A/4 + \sigma^2_D/4$ and $\sigma^2_A/4$ where σ^2_p, σ^2_A and σ^2_D are phenotypic, additive and dominance variances respectively. For this model Henderson (1985a,b) suggested, for computational convenience, two 'EM' schemes based on $\sigma^2_p - \sigma^2_A - \sigma^2_D$ and linear functions of σ^2_A and σ^2_D, that will be slower to converge.

Some of the terms involved in the differentials of L can be interpreted in terms of the quantities in mixed model equations (Henderson, 1973). Results on partitioned matrices can simplify the computation. For instance if X represents one fixed factor then X'X will be diagonal, and if p is much greater than q then it is convenient to find the prediction of b from

$$(Z'SZ + I\,g^{-1})\quad b = Z'Sy$$

or

$$Q\quad b = Z'Sy$$

where $S = I - X(X'X)^{-1}X'$ and $g = \sigma^2_b/\sigma^2$

The iterative procedure can be formulated in terms of b and Q^{-1}. In each round of the iterative procedure a different value of g is used and hence the inversion of a different qxq matrix is required.

Patterson and Thompson (1971) recognised this problem and suggested a transformation of Q into $P(D + g^{-1}I)P'$ with P orthogonal and D a diagonal matrix. Then Q^{-1} can be simply found from $P (D + g^{-1}I)^{-1}P$. This can be thought of as working with a set of n-p independent sums of squares, n-p-q+1 with expectation σ^2 and q-1 with expectation a function of σ^2, σ^2_b and D.

This fits naturally into the generalized linear model framework (McCullagh and Nelder, 1983) using the gamma distribution.

Smith and Graser (1986) suggest an attractive scheme that avoids the calculation of the latent roots D. They suggest finding an orthogonal transformation P_T such that $P_T\ Q\ P_T'$ is tridiagonal (P_T is often calculated first when P and D are found). They show that only a small number of calculations (proportional to q) are needed to give the first differentials of L once P_T is known.

For multivariate data with v traits there is an obvious extension of the model (1) when v observations are taken on each animal. The variance components σ^2 and σ^2_b being replaced by vxv symmetric matrices Σ and Σ_b. Equations of predictors will normally involve all v traits. Thompson (1982) pointed out that a canonical transformation setting up traits that are independent both genetically and phenotypically is possible and allow the predictors to be found using univariate calculations. Meyer (1985) has shown that there are simplifications in a REML procedure to estimate Σ and Σ_b by using a canonical transformation. The P_T transformation is even more useful in this multivariate case since it avoids the inversion of v qxq matrices in each round of iteration (Taylor et al,1985).

SELECTION

Not all animals used in analysis are chosen at random. Often there is either concious or unconcious selection of animals. In certain circumstances some analyses appropriate for random data are also appropriate for selected data.

Suppose there is data y_1 on some males with mean X_1 and variance V_{11}. Certain males are chosen as parents at random and observations, y_2, are taken on their offspring with mean X_2a and variance V_2 and the covariance between y_1 and y_2 is V_{12}. Then y_2 given y_1, $y_{2.1}$ has mean $X_2a - V_{21}\ V_{11}^{-1}X_1a$ and variance $V_{22} - V_{21}\ V_{11}^{-1}V_{12}$. Now if male parents are selected on the basis of y_1, then the mean and variance of y_2 change but the mean and variance of $y_{2.1}$ do not change. This argument is used by Kempthorne and von Krosigk in Henderson et al. (1959) to derive ML estimates of fixed effects and variance components when there is selection of animals and they show the estimates have the same form as when there is random selection. Thompson

(1982) reviewed other applications of this approach, pointing out that the estimating equations could be unbiased. Simulations by Rothschild et al (1979), Meyer and Thompson, (1984), Sorensen and Kennedy, (1984b) and Walter and Mao (1985) verify that likelihood methods can take some account of selection.

When selection is based on certain linear contrasts of y, say L'y, then Henderson (1975) considers using a conditional model for y given L'y and derives BLUP equations. When L'y is translation invariant (i.e. $L'(y-Xa_0)=L'y$) then these equations are identical with those when selection is at random. When L'y is not translation invariant, there are differences. If the fixed effects were known, the predictors of the random effects would have the same form as when there is random selection. However, there is a difference in the estimation of the fixed effects. For the example above, if L'y=y, then the estimates of the fixed effects depend on $y_{2.1}$ and not directly on y_1. By contrast y_1 is used in the likelihood approach and presumably could be used before the parents were selected. There are cases when $y_{2.1}$ provides little information on some fixed effects. These arguments suggest at least four methods for estimating variance components in the example above when the selection rate is not translation invariant, (i) using y_1 and y_2 (ii) using y_1 alone (iii) using $y_{2.1}$ alone, (iv) pooling y_1 and $y_{2.1}$. These alternative procedures have not been investigated.

In some ways one can expect differences between these two approaches since they are based on the statistical principles of likelihood and repeated sampling. It is well known that these alternative principles can lead to different conclusions (e.g. Cox and Hinkley, 1974). Simulation might be used to clarify some of these issues and give operational guidelines. However most, if not all, simulations have been of location invariant schemes where there is less uncertainty. We have not seen any simulation of location variant schemes. One problem is to explicitly define the class of designs that might arise in these simulations (Thompson, 1982).

SELECTION EXPERIMENTS

Some of the motivation for considering selection has been to correct for bias in farm or field data but selection can also be used to investigate the genetic structure in experimental populations. We will discuss this in the context of designing experiments to estimate multitrait genetic variances and covariances, but first some comments on selection experiments without controls seen in order given recent papers in this area (Blair and Pollak, 1984; Sorensen and Kennedy, 1984a).

In selection experiments with two divergent lines, or one selected line with a control, estimates of realised heritability can be found from comparing response to selection with cumulative selection differential (Falconer, 1981). When there is only one line without a control it is more difficult to disentangle genetic and environmental contributions. Blair and Pollak (1984) in the analysis of a sheep selection experiment calculated predictions of the genetic merit for animals born in each year. To derive an estimate of realised heritability h^2_{BP} they suggested regressing the predicted

genetic merit against the cumulative selection differential. However Thompson (1986) has shown for two simple designs without controls that h^2_{BP} is more a function of the value of heritability used to generate the predictions than the heritability in the population (see also Thompson, 1979, Dempfle, 1982). In a sense two predictions are being compared rather than a prediction with a response.

Of course other estimators of heritability could be used (Thompson, 1982, Sorensen and Kennedy, 1984b) and some involve sums of squares of predicted values. One cannot however expect these estimates to be very precise if there are no controls. For example, the information provided by parent-offspring regression is inversely proportional to the sums of squares of parental values, and if only a selected line is measured then the variance of selected parents will be small.

DESIGN OF MULTIVARIATE SELECTION EXPERIMENTS

Precise, unbiased estimates of genetic parameters, such as heritability and genetic covariance, are necessary to optimise breeding programs and to predict rates of change for various selection schemes. One experimental design objective in single trait selection experiments is to minimise the variance of heritability estimated from the regression of the mean progeny performance on that of the parent. Hill (1971) has derived equations for calculating the variances of various univariate designs, taking account of genetic drift and measurement error.

When dealing with two or more traits, the genetic variances and covariances are parameters of interest, but it is not as obvious what the optimal design objective should be when three or more parameters are considered. We suggest an objective that is symmetric for all parameters and compare the efficiencies of different selection designs. A different experimental design to the classical high-low individual selection method is examined and it is shown to be more efficient and robust.

Given a regression model $Y = X\beta + e$, where Y is the vector of the dependent variable, X is the design matrix of the independent variables and e is the vector of residuals with variance-covariance matrix V, then the confidence ellipsoid of the generalised least squares estimate $\hat{\beta}$ of β, $\hat{\beta} = (X'V^{-1}X)^{-1}X'V^{-1}Y$, with variance $(X'V^{-1}X)^{-1}$, has the form

$$[\beta : (\beta-\hat{\beta})' X'V^{-1}X (\beta-\hat{\beta}) < \text{constant}]$$

for any specified confidence coefficient. The content of the ellipsoid (e.g. volume in 3 dimensions) is proportional to $|X'V^{-1}X|^{-1/2}$. Therefore, one design criterion which we use is to minimise the content of the ellipsoid or to maximise $|X'V^{-1}X|$ the D-optimality criterion. The determinant of $X'V^{-1}X$ is denoted by DET(β). The D-optimality criterion has the useful invariance property that if a design X maximises DET(β), then the same design also maximises DET($T^*\beta$), where T^* is a full rank transformation matrix. Therefore, a design that is optimal for estimation of β is also optimal for a linear transformation, $T^*\beta$, of β. There are other overall criterion, but the do not have this invariance property.

The genetic and phenotypic variance-covariance matrices for the traits are denoted by G and P respectively. We consider cases of standardised traits, with mean zero, when the diagonal elements of the P matrix are equal to one and assume that the traits are normally distributed. The methods and designs considered can be applied to multivariate data but are

developed using bivariate data. The genetic variances and covariances of the standardised traits are then heritabilities (h_1^2 and h_2^2) and co-heritabilities ($r_A h_1 h_2$ where r_A is the genetic correlation between the two traits). In the estimation of these parameters, it is convenient to work in terms of the (3x1) vector $\beta' = 0.5\ [h_1^2\ \ r_A h_1 h_2\ \ h_2^2]$ rather than the (2x2) symmetric matrix of genetic variances and covariances.

There is no loss of generality from standardising the traits, for if the diagonal elements of the P matrix are not equal to one, then the phenotypic variables can be standardised using a transformation, T* such that the transformed G matrix becomes T*GT*'. The invariance argument of the design criterion shows that a design optimal for the parameter β is also optimal for the genetic parameters in T*GT*'.

Offspring-parent regression techniques can be used to estimate genetic parameters of more than one trait simultaneously. The standardised observations on two traits for the j-th parent and the mean of its offspring are x_{1j}, x_{2j} and $\bar{o}_{x1j}$,$\bar{o}_{x2j}$ respectively. Then

$$\begin{bmatrix}\bar{o}_{x1j}\\ \bar{o}_{x2j}\end{bmatrix} = 0.5\ GP^{-1}\begin{bmatrix}x_{1j}\\ x_{2j}\end{bmatrix} + e = 0.5\ G\begin{bmatrix}s_{1j}\\ s_{2j}\end{bmatrix} + e = \begin{bmatrix}s_{1j} & s_{2j} & 0\\ 0 & s_{1j} & s_{2j}\end{bmatrix}\beta + e$$

where s_{1j} and s_{2j} are $(x_{1j}-r_P x_{2j})/(1-r_P^2)$ and $(x_{2j}-r_P x_{1j})/(1-r_P^2)$ respectively, and r_P is the phenotypic correlation between the traits x_1 and x_2.

Assume a total of 2M unrelated individuals, of one sex in the parental generation, are measured for both traits and a proportion p_E are selected, such that $2Mp_E=4N$. We assume equal family sizes of $n=R/p_E$ progeny per family to give a total of 2MR progeny which are reared and recorded.

The parameter β can be estimated by combining the information from all 4N offspring-parent pairs. The residuals are correlated within families but not between families. The variance-covariance matrix of residuals (V) is a 8Nx8N block diagonal matrix and the only non-zero elements are a 2x2 matrix, denoted F, repeated 4N times down the diagonal. The structure of the F matrix can be derived from the univariate equations of Hill (1971) and is $F = [(0.25G-0.25GP^{-1}G) + (P-0.25G)/n]$, when family members are half-sibs. Note that the first term is the variance of a family genotypic mean about the regression (drift variance) and the second term is the variance of measurement error in the family mean value.

Investigation of DET(β) and the calculation of the inverse of V would be simpler if F was a diagonal matrix. A canonical transformation can be used to give independent traits and F would be diagonal for these canonical traits. Let S* be the transformation matrix from the original scale to the canonical scale, such that $[C_1\ C_2]' = S^*[x_1\ x_2]'$, then S* is such that S*PS*' equals the identity matrix and $S^*GS^{*\prime} = G_C$ where G_C is the diagonal variance-covariance matrix on the canonical scale. For half-sib family data, matrix F^{-1} = diag D where $d_j = [0.25\lambda_j(1-\lambda_j) + (1-0.25\lambda_j)/n]^{-1}$ and λ_j denotes the heritability of the j-th canonical trait. The expected value of DET(β_C) =

$|X'V^{-1}X_C| = d_1d_2(d_1B_2+d_2B_1)(B_1B_2-B_3^2)$ where B_1, B_2 and B_3 are the expected sums of squares and crossproducts of the observations on the canonical scale.

When using offspring-parent regression to estimate genetic parameters, the variances of the estimated genetic parameters depend on the sums of squares of the observations of the parents. When only one trait is of interest, the sum of squares is maximised by selecting individuals with high and low values to be parents (i.e. selection on individuals with extreme values). By analogy, in the two dimensional case, this suggests selecting individuals measured which are as far from the origin as possible. Invariance arguments suggest using a quadratic index of the form $(x_1\ x_2)'P^{-1}(x_1\ x_2)$ where x_j are the standardised phenotypic values. Geometrically, this can be thought of as selecting individuals outside an ellipse given by the formulae $(x_1+x_2)^2/2(1+r_P) + (x_1-x_2)^2/2(1-r_P) = w^2$, where w is chosen such that a proportion p_E of the individuals are outside the ellipse. As this ellipse used in selecting parents depends on P, we call it a phenotypic selection ellipse. Tallis (1963) considered this type of selection in a different context and derived the proportion $p_E = \exp(-w^2/2)$ and the variance-covariance matrix of the observations after elliptical selection $P^* = (1-\log p_E)\ P$.

Transformation onto the canonical scale results in the diagonalisation of the F matrix and $DET(\beta_C) = (2Mp_E)^3d_1d_2(d_1+d_2)(1-\log p_E)^3$. (2)

The phenotypic selection ellipse $(x_1\ x_2)'P^{-1}(x_1\ x_2) = w^2$ has axes x_1+x_2 and x_1-x_2. For canonical traits the selection ellipse reduces to a circle.

It is useful to compare values of $DET(\beta)$ obtained using the phenotypic selection ellipse (E) with those obtained from more conventional designs. The classical design (C) is to split individuals in the parental generation into two groups, selecting high and low within one group for trait x_1 and selecting high and low within the other group for trait x_2. An index design would use an index of both traits as the selection criteria in each group rather than selecting directly on the traits measured. We have shown (Cameron and Thompson, 1986) that indices $a_{11}x_1+a_{12}x_2$ and $a_{21}x_1+a_{22}x_2$ with the a_{ij}'s chosen such that the indices are uncorrelated and have unit phenotypic variance are reasonably efficient indices. Two pairs of such indices are $(x_1+x_2)/\sqrt{2}(1+r_P)$, $(x_1-x_2)/\sqrt{2}(1+r_P)$ and x_1, $(x_2-r_Px_1)/\sqrt{(1-r_P)}$, denoted OI for orthogonal indices. We note that any such pair of orthogonal axes can be used to generate the phenotypic selection ellipse.

For these conventional designs, the genetic parameters can be estimated using responses to selection differentials (e.g. Gunsett et al, 1984). We prefer to use offspring-parent regression as there is a gain in relative efficiency of $(1+ix)/i^2$ for the OI designs. There is still the choice

of parental traits to be used in the regression analysis. One possibility is just to use the parental selected trait for each group (i.e. for design C use x_1 in the first group and x_2 in the second group). This is similar to the usual approach with responses to selection differentials and we use this for design C. Another possibility is to use both parental traits with both groups and we use this for design OI.

For uncorrelated traits, the relative magnitudes of $DET(\beta)^{1/3}$ for the designs C, OI and E are $1+ix : 2+ix : 2(1-\log p_E)$ respectively, where i and x are the expected selection differential and abscissa on the standardised normal curve corresponding to $p_E/2$. Equal selection differentials are assumed in the two groups for classical and index designs. For example, if the selection proportion for the conventional design is 0.15, then p_E equals 0.30 and the relative magnitudes of $DET(\beta)^{1/3}$ for the designs C, OI and E are 2.61 : 3.61 : 4.41 respectively. As $DET(\beta)^{1/3}$ is inversely proportional to the variance of a genetic parameter estimate on the canonical scale, the above values of $DET(\beta)^{1/3}$ show a marked increase in precision of the elliptical design compared with conventional designs (C or OI).

Formula for comparing C designs with OI designs are more complicated for correlated traits, but examination of the formula suggest that for correlated traits design C will be even less efficient than design OI than when the traits are uncorrelated. For orthogonal designs, the weights given to the traits x_1+x_2 and x_1-x_2 are $1/\sqrt{2(1+r_P)}$ and $1/\sqrt{2(1-r_P)}$. By contrast, the classical design gives equal weight to x_1+x_2 and x_1-x_2. As r_P deviates from zero, the relative efficiency of design C compared with design OI decreases. Numerical examples in Cameron and Thompson (1986) illustrate this point and also show the advantage of using orthogonal indices.

Optimising the selection proportion for various designs

If the canonical heritabilities are equal, say to λ, the optimum proportion to select for maximising $DET(\beta)$ with different selection designs can be found by differentiation of $DET(\beta)$ with respect to p. When using a conventional design (designs I and C), p satisfies $(1-0.25\lambda)/0.25R\lambda(1-\lambda) = (1+x^2)/2p(1+ix-x^2)$ which is similar to the appropriate equation of Hill and Thompson (1977) derived in a univariate context. When using a phenotypic selection ellipse, p_E satisfies $(1-0.25\lambda)/0.25R\lambda(1-\lambda) = -\log p_E/p_E$.

These equations give an optimal design for fixed numbers of individuals in the parental, 2M, and offspring, 2MR, generations. If the balance of individuals in the two generations can be adjusted, R, then the optimal value of $DET(\beta)/(2M(1+R))^3$, a measure of the efficiency of the design on a per individual measured basis, can be determined. The optimum value occurs when p_E satisfies $(1-0.25\lambda)/0.25\lambda(1-\lambda) = (\log p_E)^2/p_E$ and $R = -\log p_E$.

Since the genetic parameters are not known "a priori", designs should be robust to poor estimates of these parameters. Hill and Thompson (1977) showed that their univariate designs were robust and Cameron and Thompson (1986) show similar results hold for bivariate designs. For example, when R equals 2.0, λ values in the ranges (0.18, 0.87) and (0.13, 0.90) and designs

using p_E=0.20 are at least 0.90 and 0.95 as efficient as the optimal design.

When the canonical heritabilities are unequal, one suggestion is to use a pooled value of λ, with λ chosen such that the resulting d value satisfies $2d^3 = d_1 d_2$ (see equation (2)). As there are two solutions

to the quadratic equation for λ, we suggest using the λ value that lies between λ_1 and λ_2. The resulting value of λ is essentially independent of

the value of n, the family size, when n is moderate (n>15). Numerical comparisons showed that using the derived λ value is reasonable when the canonical heritabilities are unequal.

We have demonstrated the theory using selected parents of one sex. There have been gains from using assortative mating when estimating genetic parameters for a single trait (Reeve, 1955). There will be similar gains from multivariate designs, with selection of mates being based on minimising the "phenotypic distance" between mates. The multivariate design theory naturally extends to more than two traits and more than two generations.

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