

Lecture 8:
Mixed Model estimates of
genetic parameters:
BLUP (genetic effects) and
REML (genetic variances)

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Estimation of $\text{Var}(A)$ and Breeding Values in General Pedigrees

The classic designs (ANOVA, P-O regression) for estimating variance components are simple, involving only a single type of relative comparison. Further, they assume balanced designs, with the number of offspring the same in each family.

In the real world, we often have a pedigree of relatives, with a very unbalanced design. Fortunately, the general mixed model (so called because it includes both fixed and random effects), offers an ideal platform for both estimating genetic variances as well as predicting the breeding values of individuals.

Almost all animal breeding is based on such models, with **REML** (restricted max likelihood) used to estimate variances and **BLUP** (best linear unbiased predictors) used to predict BVs.

BLUP in plant breeding

- BLUP has migrated from animal breeding into plant breeding.
- Advantages:
 - Handles unbalanced designs
 - Uses information for all relatives measured to improve estimates
- BLUP can be used to estimate a variety of genetic values
 - *GCA*, *SCA*, line values (i.e., genotypic values of pure lines)
 - One can also use BLUP machinery to estimate environmental effects, $G \times E$

The general mixed model

Vector of fixed effects (to be estimated),
e.g., year, location and treatment effects

Vector of
observations
(phenotypes)

Incidence matrix for random effects

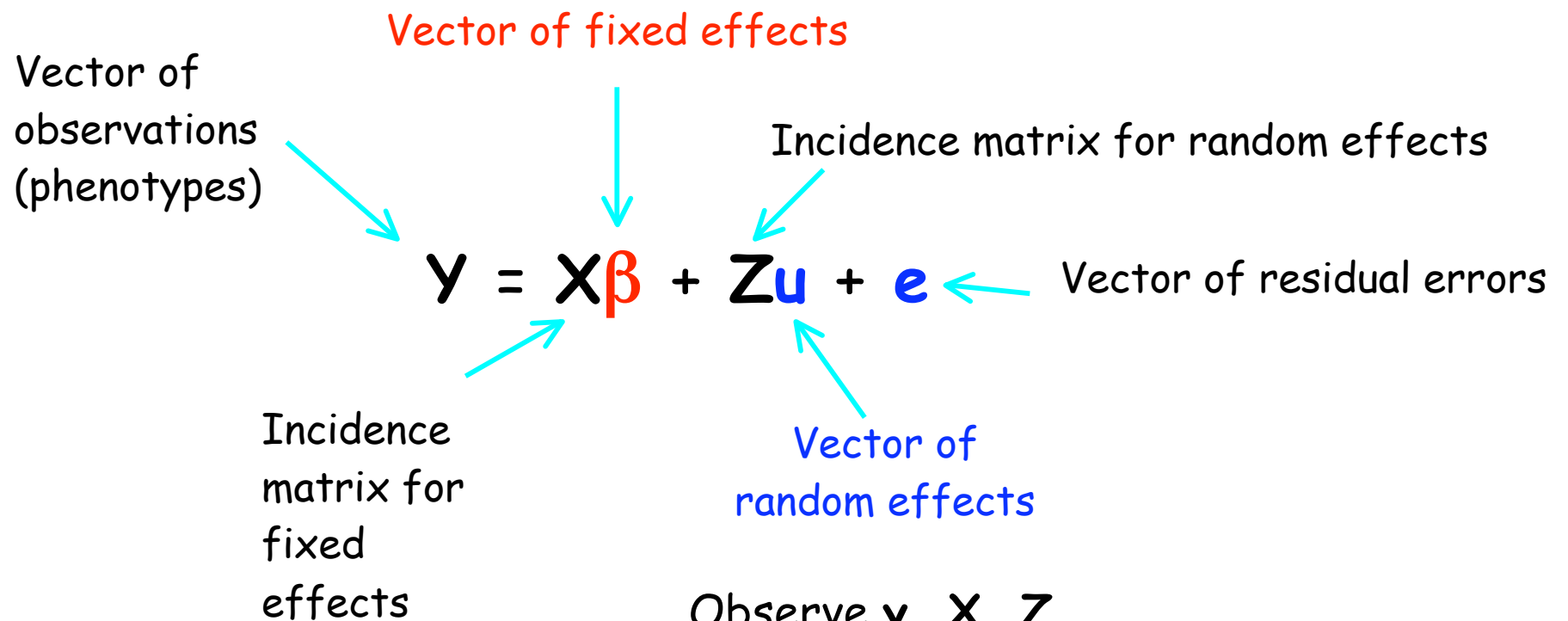
$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

Vector of residual errors
(random effects)

Incidence
matrix for
fixed
effects

Vector of
random effects,
such as individual
genetic values
(to be estimated)

The general mixed model



Observe \mathbf{y} , \mathbf{X} , \mathbf{Z} .

Estimate fixed effects $\boldsymbol{\beta}$

Predict random effects \mathbf{u} , \mathbf{e}

Example

Suppose we wish to estimate the breeding values of three sires (fathers), each of which is mated to a random female (dam), producing two offspring, some reared in environment one, others in environment two. The data are

| Observation | Value | Sire | environment |
|-------------|-------|------|-------------|
| Y_{111} | 9 | 1 | 1 |
| Y_{121} | 12 | 1 | 2 |
| Y_{211} | 11 | 2 | 1 |
| Y_{212} | 6 | 2 | 1 |
| Y_{311} | 7 | 3 | 1 |
| Y_{321} | 14 | 3 | 2 |

Here the basic model is

$$y_{ijk} = \beta_j + u_i + e_{ijk}$$

Effect of environment j

Breeding value of sire i

$$\mathbf{y} = \begin{pmatrix} y_{1,1,1} \\ y_{1,2,1} \\ y_{2,1,1} \\ y_{2,1,2} \\ y_{3,1,1} \\ y_{3,2,1} \end{pmatrix} = \begin{pmatrix} 9 \\ 12 \\ 11 \\ 6 \\ 7 \\ 14 \end{pmatrix}$$

The mixed model vectors and matrices become

$$\mathbf{X} = \begin{pmatrix} 1 & 0 \\ 0 & 1 \\ 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \end{pmatrix}, \quad \mathbf{Z} = \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 1 \end{pmatrix}, \quad \boldsymbol{\beta} = \begin{pmatrix} \beta_1 \\ \beta_2 \end{pmatrix}, \quad \mathbf{u} = \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix}$$

Means & Variances for $y = X\beta + Zu + e$

Means: $E(u) = E(e) = 0$, $E(y) = X\beta$

Variances:

Let R be the covariance matrix for the residuals. We typically assume $R = \sigma_e^2 * I$

Let G be the covariance matrix for the breeding values (the vector u)

The covariance matrix for y becomes

$$V = ZGZ^T + R$$

Effects of model misspecification

Suppose we simply used a General Linear model (only fixed effects) for this example?

Here $y = X\beta + e^*$, where $e^* \sim \text{MVN}(0, V)$, implying $y \sim \text{MVN}(X\beta, V)$

The effect of using a mixed model is that it partitions the residual e^* as

$$e^* = Zu + e$$

While e^* is assumed to have a simple covariance structure ($\sigma_e^2 \mathbf{I}$), correlations among the random effects u compromise this assumption. We can account for these through $\text{Cov}(u)$ by adding u to the model 9

Estimating fixed Effects & Predicting Random Effects

For a mixed model, we observe \mathbf{y} , \mathbf{X} , and \mathbf{Z}
 β , \mathbf{u} , \mathbf{R} , and \mathbf{G} are generally unknown

Two complementary estimation issues

(i) Estimation of β and \mathbf{u}

$$\hat{\beta} = (\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{V}^{-1} \mathbf{y} \quad \text{Estimation of fixed effects}$$

BLUE = Best Linear Unbiased Estimator

$$\hat{\mathbf{u}} = \mathbf{GZ}^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\hat{\beta}) \quad \text{Prediction of random effects}$$

BLUP = Best Linear Unbiased Predictor

$$\text{Recall } \mathbf{V} = \mathbf{ZGZ}^T + \mathbf{R}$$

Let's return to our example

Assume residuals uncorrelated & homoscedastic,
 $R = \sigma_e^2 * I$. Hence, need σ_e^2 to solve BLUE/BLUP equations.

Suppose $\sigma_e^2 = 6$, giving $R = 6 * I$

Now consider G , the covariance matrix for u (the vector of the three sire breeding values). Assume the sires are unrelated, so G is diagonal with element $\sigma_G^2 =$ sire variance, where $\sigma_G^2 = \sigma_A^2 / 4$.

Suppose $\sigma_A^2 = 8$, giving $G = 8/4 * I$

Solving, recalling that $\mathbf{V} = \mathbf{ZGZ}^T + \mathbf{R}$

$$\mathbf{V} = \frac{8}{4} \begin{pmatrix} 1 & 0 & 0 \\ 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} 1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 \end{pmatrix} + 6 \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

$$= \begin{pmatrix} 8 & 2 & 0 & 0 & 0 & 0 \\ 2 & 8 & 0 & 0 & 0 & 0 \\ 0 & 0 & 8 & 2 & 0 & 0 \\ 0 & 0 & 2 & 8 & 0 & 0 \\ 0 & 0 & 0 & 0 & 8 & 2 \\ 0 & 0 & 0 & 0 & 2 & 8 \end{pmatrix} \quad \text{giving} \quad \mathbf{V}^{-1} = \frac{1}{30} \begin{pmatrix} 4 & -1 & 0 & 0 & 0 & 0 \\ -1 & 4 & 0 & 0 & 0 & 0 \\ 0 & 0 & 4 & -1 & 0 & 0 \\ 0 & 0 & -1 & 4 & 0 & 0 \\ 0 & 0 & 0 & 0 & 4 & -1 \\ 0 & 0 & 0 & 0 & -1 & 4 \end{pmatrix}$$

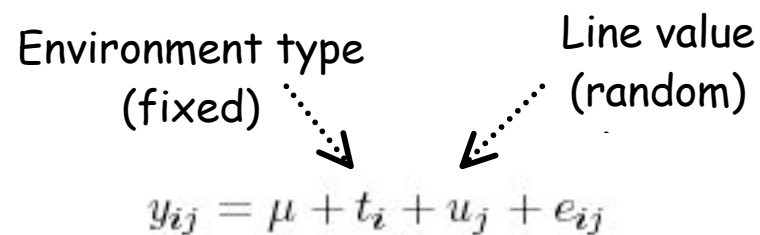
$$\hat{\boldsymbol{\beta}} = \begin{pmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \end{pmatrix} = (\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{V}^{-1} \mathbf{y} = \frac{1}{18} \begin{pmatrix} 148 \\ 235 \end{pmatrix}$$

$$\hat{\mathbf{u}} = \begin{pmatrix} \hat{u}_1 \\ \hat{u}_2 \\ u_3 \end{pmatrix} = \mathbf{GZ}^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\hat{\boldsymbol{\beta}}) = \frac{1}{18} \begin{pmatrix} -1 \\ 2 \\ -1 \end{pmatrix}$$

BLUP estimates of line values

Bernardo example (11.3.1): yield in four (related) inbred lines of Barley raised over two sets of environments

| Envir | <i>n</i> | Cultivar | yeild |
|-------|----------|----------|-------|
| 1 | 18 | Morex | 4.45 |
| 1 | 18 | Robust | 4.61 |
| 1 | 18 | Stander | 5.27 |
| 2 | 9 | Robust | 5.00 |
| 2 | 9 | Excel | 5.82 |
| 2 | 9 | Stander | 5.79 |



Model $y = \mathbf{Xb} + \mathbf{Zu} + \mathbf{e}, \quad \mathbf{u} \sim MVN(\mathbf{0}, \mathbf{G}), \quad \mathbf{e} \sim MVN(\mathbf{0}, \mathbf{R})$

| Envir | <i>n</i> | Cultivar | yeild |
|-------|----------|----------|-------|
| 1 | 18 | Morex | 4.45 |
| 1 | 18 | Robust | 4.61 |
| 1 | 18 | Stander | 5.27 |
| 2 | 9 | Robust | 5.00 |
| 2 | 9 | Excel | 5.82 |
| 2 | 9 | Stander | 5.79 |

$$b_i = \mu + t_i$$

Line values

$$\begin{pmatrix} 4.45 \\ 4.61 \\ 5.27 \\ 5.00 \\ 5.82 \\ 5.79 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 1 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} b_1 \\ b_2 \end{pmatrix} + \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \\ u_4 \end{pmatrix} + \begin{pmatrix} e_{11} \\ e_{12} \\ e_{14} \\ e_{22} \\ e_{23} \\ e_{24} \end{pmatrix}$$

$$\text{Var}(\mathbf{u}) = \mathbf{G} = 2\sigma_A^2 \begin{pmatrix} 1 & 0.5 & 0.44 & 0.34 \\ 0.5 & 1 & 0.84 & 0.67 \\ 0.44 & 0.84 & 1 & 0.71 \\ 0.34 & 0.67 & 0.71 & 1 \end{pmatrix}, \quad \text{Var}(\mathbf{e}) = \mathbf{G} = \mathbf{R} = \frac{\sigma_e^2}{18} \begin{pmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 2 & 0 & 0 \\ 0 & 0 & 0 & 0 & 2 & 0 \\ 0 & 0 & 0 & 0 & 0 & 2 \end{pmatrix}$$

Relationship values (from pedigree data on how lines are related)

Observations differ in their residual error due to sample size differences

Henderson's Mixed Model Equations

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}, \quad \mathbf{u} \sim (\mathbf{0}, \mathbf{G}), \quad \mathbf{e} \sim (\mathbf{0}, \mathbf{R}), \quad \text{cov}(\mathbf{u}, \mathbf{e}) = \mathbf{0},$$

If \mathbf{X} is $n \times p$ and \mathbf{Z} is $n \times q$

$$\begin{array}{cc} p \times p & p \times q \\ \left(\begin{array}{cc} \mathbf{X}^T \mathbf{R}^{-1} \mathbf{X} & \mathbf{X}^T \mathbf{R}^{-1} \mathbf{Z} \\ \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{X} & \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{Z} + \mathbf{G}^{-1} \end{array} \right) & \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{u}} \end{pmatrix} = \begin{pmatrix} \mathbf{X}^T \mathbf{R}^{-1} \mathbf{y} \\ \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{y} \end{pmatrix} \\ q \times p & q \times q \end{array}$$

The whole matrix is $(p+q) \times (p+q)$

Easier to numerically work
with than BLUP/BLUE
equations

$$\hat{\boldsymbol{\beta}} = (\mathbf{X}^T \mathbf{V}^{-1} \mathbf{X})^{-1} \mathbf{X}^T \mathbf{V}^{-1} \mathbf{y}$$

$$\hat{\mathbf{u}} = \mathbf{GZ}^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\hat{\boldsymbol{\beta}})$$

$$\mathbf{V} = \mathbf{ZGZ}^T + \mathbf{R}$$



Inversion of an $n \times n$ matrix

Standard Errors

A relatively straightforward extension of Henderson's mixed-model equations provides estimates of the standard errors of the fixed and random effects. Let the inverse of the leftmost matrix in Equation 26.5 be

$$\begin{pmatrix} \mathbf{X}^T \mathbf{R}^{-1} \mathbf{X} & \mathbf{X}^T \mathbf{R}^{-1} \mathbf{Z} \\ \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{X} & \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{Z} + \mathbf{G}^{-1} \end{pmatrix}^{-1} = \begin{pmatrix} \mathbf{C}_{11} & \mathbf{C}_{12} \\ \mathbf{C}_{12}^T & \mathbf{C}_{22} \end{pmatrix} \quad (26.6)$$

where \mathbf{C}_{11} , \mathbf{C}_{12} , and \mathbf{C}_{22} are, respectively, $p \times p$, $p \times q$, and $q \times q$ submatrices. Using this notation, Henderson (1975) showed that the sampling covariance matrix for the BLUE of $\boldsymbol{\beta}$ is given by

$$\boldsymbol{\sigma}(\hat{\boldsymbol{\beta}}) = \mathbf{C}_{11} \quad (26.7a)$$

that the sampling covariance matrix of the prediction errors ($\hat{\mathbf{u}} - \mathbf{u}$) is given by

$$\boldsymbol{\sigma}(\hat{\mathbf{u}} - \mathbf{u}) = \mathbf{C}_{22} \quad (26.7b)$$

and that the sampling covariance of estimated effects and prediction errors is given by

$$\boldsymbol{\sigma}(\hat{\boldsymbol{\beta}}, \hat{\mathbf{u}} - \mathbf{u}) = \mathbf{C}_{12} \quad (26.7c)$$

(We consider $\hat{\mathbf{u}} - \mathbf{u}$ rather than $\hat{\mathbf{u}}$ as the latter includes variance from both the prediction error and the random effects \mathbf{u} themselves.)

Let's redo our example on slide 6 using Henderson's Equation

$$\mathbf{X}^T \mathbf{R}^{-1} \mathbf{X} = \frac{1}{6} \begin{pmatrix} 4 & 0 \\ 0 & 2 \end{pmatrix}, \quad \mathbf{X}^T \mathbf{R}^{-1} \mathbf{Z} = \left(\mathbf{Z}^T \mathbf{R}^{-1} \mathbf{X} \right)^T = \frac{1}{6} \begin{pmatrix} 1 & 2 & 1 \\ 1 & 0 & 1 \end{pmatrix}$$

$$\mathbf{G}^{-1} + \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{Z} = \frac{5}{6} \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad \mathbf{X}^T \mathbf{R}^{-1} \mathbf{y} = \frac{1}{6} \begin{pmatrix} 33 \\ 26 \end{pmatrix}, \quad \mathbf{Z}^T \mathbf{R}^{-1} \mathbf{y} = \frac{1}{6} \begin{pmatrix} 21 \\ 17 \\ 21 \end{pmatrix}$$

$$\begin{pmatrix} 4 & 0 & 1 & 2 & 1 \\ 0 & 2 & 1 & 0 & 1 \\ 1 & 1 & 5 & 0 & 0 \\ 2 & 0 & 0 & 5 & 0 \\ 1 & 1 & 0 & 0 & 5 \end{pmatrix} \begin{pmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \\ \hat{u}_1 \\ \hat{u}_2 \\ \hat{u}_3 \end{pmatrix} = \begin{pmatrix} 33 \\ 26 \\ 21 \\ 17 \\ 21 \end{pmatrix}$$

Taking the inverse gives

$$\begin{pmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \\ \hat{u}_1 \\ \hat{u}_2 \\ \hat{u}_3 \end{pmatrix} = \frac{1}{18} \begin{pmatrix} 148 \\ 235 \\ -1 \\ 2 \\ -1 \end{pmatrix}$$

As found above

The Animal Model, $y_i = \mu + a_i + e_i$

Here, the individual is the unit of analysis, with y_i the phenotypic value of the individual and a_i its BV

$$\mathbf{X} = \begin{pmatrix} 1 \\ 1 \\ \vdots \\ 1 \end{pmatrix}, \quad \beta = \mu, \quad \mathbf{u} = \begin{pmatrix} a_1 \\ a_2 \\ \vdots \\ a_k \end{pmatrix} \quad \mathbf{G} = \sigma_A^2 \mathbf{A},$$

Where the **additive genetic relationship matrix** \mathbf{A} is given by

$A_{ij} = 2\theta_{ij}$, namely twice the coefficient of coancestry

Assume $\mathbf{R} = \sigma_e^2 * \mathbf{I}$, so that $\mathbf{R}^{-1} = 1/(\sigma_e^2) * \mathbf{I}$.

Likewise, $\mathbf{G} = \sigma_A^2 * \mathbf{A}$, so that $\mathbf{G}^{-1} = 1/(\sigma_A^2) * \mathbf{A}^{-1}$.

The "animal" model estimates the breeding value for each individual, even for a plant or tree! Same approach also works to estimate line (genotypic) values for inbreds.

Returning to the animal model

Henderson's mixed model equations

$$\begin{pmatrix} \mathbf{X}^T \mathbf{X} & \mathbf{X}^T \mathbf{Z} \\ \mathbf{Z}^T \mathbf{X} & \mathbf{Z}^T \mathbf{Z} + \lambda \mathbf{A}^{-1} \end{pmatrix} \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{u}} \end{pmatrix} = \begin{pmatrix} \mathbf{X}^T \mathbf{y} \\ \mathbf{Z}^T \mathbf{y} \end{pmatrix}$$

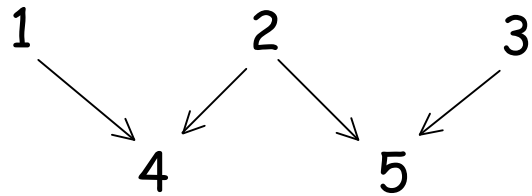
here $\lambda = \sigma_e^2 / \sigma_A^2 = (1-h^2)/h^2$

This reduces to

$$\begin{pmatrix} n & \mathbf{1}^T \\ \mathbf{1} & \mathbf{I} + \lambda \mathbf{A}^{-1} \end{pmatrix} \begin{pmatrix} \hat{\mu} \\ \hat{\mathbf{u}} \end{pmatrix} = \begin{pmatrix} \sum^n y_i \\ \mathbf{y} \end{pmatrix}$$

Example

Suppose our pedigree is



$$\mathbf{A} = \begin{pmatrix} 1 & 0 & 0 & 1/2 & 0 \\ 0 & 1 & 0 & 1/2 & 1/2 \\ 0 & 0 & 1 & 0 & 1/2 \\ 1/2 & 1/2 & 0 & 1 & 1/4 \\ 0 & 1/2 & 1/2 & 1/4 & 1 \end{pmatrix}$$

Suppose $\lambda = 1$ (corresponds to $h^2 = 0.5$). In this case,

$$\mathbf{I} + \lambda \mathbf{A}^{-1} = \begin{pmatrix} 5/2 & 1/2 & 0 & -1 & 0 \\ 1/2 & 3 & 1/2 & -1 & -1 \\ 0 & 1/2 & 5/2 & 0 & -1 \\ -1 & -1 & 0 & 3 & 0 \\ 0 & -1 & -1 & 0 & 3 \end{pmatrix}$$

Suppose the vector of observations is

$$y = \begin{pmatrix} y_1 \\ y_2 \\ y_3 \\ y_4 \\ y_5 \end{pmatrix} = \begin{pmatrix} 7 \\ 9 \\ 10 \\ 6 \\ 9 \end{pmatrix}$$

Here $n = 5$, $\sum y = 41$, and Henderson's equation becomes

$$\begin{pmatrix} 5 & 1 & 1 & 1 & 1 & 1 \\ 1 & 5/2 & 1/2 & 0 & -1 & 0 \\ 1 & 1/2 & 3 & 1/2 & -1 & -1 \\ 1 & 0 & 1/2 & 5/2 & 0 & -1 \\ 1 & -1 & -1 & 0 & 3 & 0 \\ 1 & 0 & -1 & -1 & 0 & 3 \end{pmatrix} \begin{pmatrix} \hat{\mu} \\ \hat{a}_1 \\ \hat{a}_2 \\ \hat{a}_3 \\ \hat{a}_4 \\ \hat{a}_5 \end{pmatrix} = \begin{pmatrix} 41 \\ 7 \\ 9 \\ 10 \\ 6 \\ 9 \end{pmatrix}$$

Solving gives

$$\hat{\mu} = \frac{440}{53} \simeq 8.302, \quad \begin{pmatrix} \hat{a}_1 \\ \hat{a}_2 \\ \hat{a}_3 \\ \hat{a}_4 \\ \hat{a}_5 \end{pmatrix} = \begin{pmatrix} -662/689 \\ 4/53 \\ 610/689 \\ -732/689 \\ 381/689 \end{pmatrix} \simeq \begin{pmatrix} -0.961 \\ 0.076 \\ 0.885 \\ -1.062 \\ 0.553 \end{pmatrix}$$

More on the animal model

- Under the animal model
 - $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{e}$
 - $\mathbf{a} \sim (0, \sigma_A^2 \mathbf{A}), \mathbf{e} \sim (0, \sigma_e^2 \mathbf{I})$
 - $\text{BLUP}(\mathbf{a}) = \sigma_A^2 \mathbf{A}\mathbf{Z}^T \mathbf{V}^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$
 - Where $\mathbf{V} = \mathbf{Z}\mathbf{G}\mathbf{Z}^T + \mathbf{R} = \sigma_A^2 \mathbf{Z}\mathbf{A}\mathbf{Z}^T + \sigma_e^2 \mathbf{I}$
- Consider the simplest case of a single observation on one individual, where the only fixed effect is the mean μ , which is assumed known
 - Here $\mathbf{Z} = \mathbf{A} = \mathbf{I} = (1)$,
 - $\mathbf{V} = \sigma_A^2 + \sigma_e^2$
 - $\sigma_A^2 \mathbf{A}\mathbf{Z}^T \mathbf{V}^{-1} = \sigma_A^2 / (\sigma_A^2 + \sigma_e^2) = h^2$
 - $\text{BLUP}(\mathbf{a}) = h^2 (\mathbf{y} - \mu)$

- More generally, with single observations on n unrelated individuals,
 - $A = Z = \mathbf{I}_{n \times n}$
 - $V = \sigma_A^2 \mathbf{ZAZ}^T + \sigma_e^2 \mathbf{I} = (\sigma_A^2 + \sigma_e^2) \mathbf{I}$
 - $\sigma_A^2 \mathbf{AZ}^T V^{-1} = h^2 \mathbf{I}$
 - $BLUP(\mathbf{a}) = \sigma_A^2 \mathbf{AZ}^T V^{-1}(\mathbf{y} - \mathbf{X}\beta) = h^2 (\mathbf{y} - \mu)$
- Hence, the predicted breeding value of individual i is just $BLUP(a_i) = h^2 (y_i - \mu)$
- When at least some individuals are related and/or inbred (so that $A \neq \mathbf{I}$) and/or missing or multiple records (so that $Z \neq \mathbf{I}$), then the estimates of the BV differ from this simple form, but BLUP fully accounts for this.

BLUP is a shrinkage estimator

- For a single observation on one individual, $BLUP(a) = h^2(y - \mu)$
 - The difference between the observed value (y) and the mean (μ) is shrunk by the factor h^2 --- shrinks the estimate back towards the mean (zero in the case of BVs)
- More generally, $BLUP(a) = GZ^TV^{-1}(y - X\beta)$
 - First adjusts observations (y) for fixed effects ($X\beta$) and then regresses this difference back towards zero (the mean BV), as Cov^*Var^{-1} is a generalized regression coefficient

The Relationship Matrix A

- Recall $\text{Cov}(A_i, A_j) = 2\theta_{ij}$ $\text{Var}(A) = \text{Var}(A)^* A_{ij}$
- Typically given from a pedigree, but increasingly being estimated from marker data
- The diagonal elements indicate the amount of inbreeding
 - $A_{ii} = 1 + f_i$, where f_i is inbreeding coefficient for individual i .
 - For a fully-inbred, $A_{ii} = 2$

Marker-based relationship matrices

- There are two reasons for using a marker-estimated relationship matrix
 - Pedigree either unknown or poorly known
 - With very dense markers, provides a better estimate than a known pedigree. Why?
 - Consider two (non-inbred) full-sibs. The expectation under a pedigree is that they share exactly half their genes.
 - However, there is a **sampling variance** about this expected value, so that some pair of sibs may share more than 50%, while others share less. Using markers to detect such pairs improves the estimated values.
 - This is called **G-BLUP** (in animal breeding) and is a form of **genomic selection**

Marker-based relationship matrix

Simplest case is to consider a very large number (L) of SNPs, and treat alike in state as IBD, and then compute the probability q_{xy} that x and y share a randomly-drawn allele for each SNP marker. Twice the average over all markers is the entry for x and y in the relationship matrix (as $A_{xy} = 2q_{xy}$)

SNP genotype for x

| | | | |
|----------------------------|-----|-----|-----|
| | 00 | 01 | 11 |
| SNP genotype for y 00 | 1 | 0.5 | 0 |
| 01 | 0.5 | 0.5 | 0.5 |
| 11 | 0 | 0.5 | 1 |

Values for q_{xy} given the SNP genotypes

Estimation of R and G

A second estimation issue concerns the covariance matrix for residuals R and for breeding values G

As we have seen, both matrices have the form $\sigma^2 * B$, where the variance σ^2 is unknown, but the matrix B of constants is known

For example, for residuals, $R = \sigma_e^2 * I$

For breeding values, $G = \sigma_A^2 * A$, where A is given from the pedigree

REML Variance Component Estimation


REML = Restricted Maximum Likelihood.

Standard ML variance estimation assumes fixed factors are known without error. Results in **downward bias** in variance estimates

REML maximizes that portion of the likelihood that does not depend on fixed effects

Basic idea: Use a transformation to remove fixed effect, then perform ML on this transformed vector

Simple variance estimate under ML vs. REML

$$ML = \frac{1}{n} \sum_{i+1}^n (x - \bar{x})^2, \quad REML = \frac{1}{n-1} \sum_{i+1}^n (x - \bar{x})^2$$


REML adjusts for the
estimated fixed
effect,
in this case, the mean

With balanced design, ANOVA variance estimates are
equivalent to REML variance estimates

Multiple random effects

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{W}\mathbf{u} + \mathbf{e}$$

\mathbf{y} is a $n \times 1$ vector of observations

$\boldsymbol{\beta}$ is a $q \times 1$ vector of *fixed effects*

\mathbf{a} is a $p \times 1$ vector of *random effects*

\mathbf{u} is a $m \times 1$ vector of *random effects*

\mathbf{X} is $n \times q$, \mathbf{Z} is $n \times p$, \mathbf{W} is $n \times m$

\mathbf{y} , \mathbf{X} , \mathbf{Z} , \mathbf{W} observed. $\boldsymbol{\beta}$, \mathbf{a} , \mathbf{u} , \mathbf{e} to be estimated

Covariance structure

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{W}\mathbf{u} + \mathbf{e}$$

Defining the covariance structure key in any mixed-model

Suppose $\mathbf{e} \sim (0, \sigma_e^2 \mathbf{I})$, $\mathbf{u} \sim (0, \sigma_u^2 \mathbf{I})$, $\mathbf{a} \sim (0, \sigma_A^2 \mathbf{A})$,
as with breeding values

These covariances matrices are still not sufficient, as we have yet to describe the relationship between \mathbf{e} , \mathbf{a} , and \mathbf{u} . If they are **independent**:

$$\begin{pmatrix} \mathbf{a} \\ \mathbf{u} \\ \mathbf{e} \end{pmatrix} \sim \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \sigma_A^2 \cdot \mathbf{A} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \sigma_u^2 \cdot \mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \sigma_e^2 \cdot \mathbf{I} \end{pmatrix}$$

$$\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{W}\mathbf{u} + \mathbf{e} \quad \begin{pmatrix} \mathbf{a} \\ \mathbf{u} \\ \mathbf{e} \end{pmatrix} \sim \begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \sigma_A^2 \cdot \mathbf{A} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \sigma_u^2 \cdot \mathbf{I} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \sigma_e^2 \cdot \mathbf{I} \end{pmatrix}$$

Covariance matrix for the vector of observations \mathbf{y}

$$\text{Var}(\mathbf{y}) = \mathbf{V} = \mathbf{Z}\mathbf{A}\mathbf{Z}^T \sigma_A^2 + \mathbf{W}\mathbf{W}^T \sigma_u^2 + \mathbf{I} \sigma_e^2$$

Note that if we ignored the second vector \mathbf{u} of random effects, and assumed $\mathbf{y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{a} + \mathbf{e}^*$, then $\mathbf{e}^* = \mathbf{W}\mathbf{u} + \mathbf{e}$, with $\text{Var}(\mathbf{e}^*) = \sigma_e^2 \mathbf{I} + \sigma_u^2 \mathbf{W}\mathbf{W}^T$

Consequence of ignoring random effects is that these are incorporated into the residuals, potentially compromising its covariance structure

Mixed-model Equations

$$\begin{pmatrix} \mathbf{X}^T \mathbf{X} & \mathbf{X}^T \mathbf{Z} & \mathbf{X}^T \mathbf{W} \\ \mathbf{Z}^T \mathbf{X} & \mathbf{Z}^T \mathbf{Z} + \lambda_A \mathbf{A}^{-1} & \mathbf{Z}^T \mathbf{W} \\ \mathbf{W}^T \mathbf{X} & \mathbf{W}^T \mathbf{Z} & \mathbf{W}^T \mathbf{W} + \lambda_u \mathbf{I} \end{pmatrix} \begin{pmatrix} \hat{\boldsymbol{\beta}} \\ \hat{\mathbf{a}} \\ \hat{\mathbf{u}} \end{pmatrix} = \begin{pmatrix} \mathbf{X}^T \mathbf{y} \\ \mathbf{Z}^T \mathbf{y} \\ \mathbf{W}^T \mathbf{y} \end{pmatrix}$$

where

$$\lambda_A = \frac{\sigma_e^2}{\sigma_A^2} \quad \text{and} \quad \lambda_u = \frac{\sigma_e^2}{\sigma_u^2}$$

Generalizing BLUP

- Thus far, we have framed BLUP in the standard animal breeding context which estimates a vector of breeding values from the genetic relationship matrix
- More generally, we can estimate any number of vectors g of genetic parameters (such as CGA, SCA, line values) given some matrix of genetic relatedness
- Historically the relatedness matrix is obtained from a pedigree, but now with dense markers it can be estimated directly
 - Esp. important when using a set of lines with a poor historical pedigree of their relationships ³⁵

BLUP for GCA, SCA

Again, Example from Bernardo (11.5.1)

B73, B84, and H123 are in one maize heterotic group (Stiff Stalk),
Mo17 and N197 in another (Lancaster)

| Envir | Cross | yeild |
|-------|-------------|-------|
| 1 | B73 × Mo17 | 7.85 |
| 1 | H123 × Mo17 | 7.36 |
| 1 | B84 × N197 | 5.61 |
| 2 | H123 × Mo17 | 7.47 |
| 2 | B84 × N197 | 5.96 |

Note highly unbalanced
design --- not all crosses
in both environments

$$y_{ijk} = \mu + t_k + GCA_i + GCA_j + SCA_{i,j} + e_{ijk}$$

$$y = \mathbf{Xb} + \mathbf{Z}_1\mathbf{g} + \mathbf{Z}_2\mathbf{s} + \mathbf{e}, \quad \text{Var} \begin{pmatrix} \mathbf{g} \\ \mathbf{s} \\ \mathbf{e} \end{pmatrix} \sim MVN \left(\begin{pmatrix} \mathbf{0} \\ \mathbf{0} \\ \mathbf{0} \end{pmatrix}, \begin{pmatrix} \mathbf{G} & \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \mathbf{S} & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \mathbf{R} \end{pmatrix} \right)$$

| Envir | Cross | yeild |
|-------|--------------|-------|
| 1 | B73 × Mol17 | 7.85 |
| 1 | H123 × Mol17 | 7.36 |
| 1 | B84 × N197 | 5.61 |
| 2 | H123 × Mol17 | 7.47 |
| 2 | B84 × N197 | 5.96 |

$$\begin{pmatrix} 7.85 \\ 7.36 \\ 5.61 \\ 7.47 \\ 5.96 \end{pmatrix} = \begin{pmatrix} 1 & 0 \\ 1 & 0 \\ 1 & 0 \\ 0 & 1 \\ 0 & 1 \end{pmatrix} \begin{pmatrix} b_1 \\ b_2 \end{pmatrix} + \begin{pmatrix} 1 & 0 & 0 & 1 & 0 \\ 0 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 \\ 0 & 0 & 1 & 1 & 0 \\ 0 & 1 & 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} GCA_{B73} \\ GCA_{B84} \\ GCA_{H123} \\ GCA_{Mol17} \\ GCA_{N197} \end{pmatrix} + \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \begin{pmatrix} SCA_{B73 \times Mol17} \\ SCA_{H123 \times Mol17} \\ SCA_{B84 \times N197} \end{pmatrix} + \mathbf{e}$$

$$\text{Var}(\mathbf{g}) = \mathbf{G} = \sigma_{GCA}^2 \begin{pmatrix} 1 & 0.27 & 0.75 & 0 & 0 \\ 0.27 & 1 & 0.20 & 0 & 0 \\ 0.75 & 0.2 & 1 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0.75 \\ 0 & 0 & 0 & 0.75 & 1 \end{pmatrix}, \quad \text{Var}(\mathbf{s}) = \mathbf{S} = \sigma_{SCA}^2 \begin{pmatrix} 1 & 0.75 & 0.2 \\ 0.75 & 1 & 0.15 \\ 0.20 & 0.15 & 1 \end{pmatrix}$$

Covariance matrix based on pedigree information (see Bernardo for details)