Lecture 1 - A brief introduction to mixed models

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Outline

Part 1: Concepts

- History of mixed models
- Mixed models in plant breeding
- Fixed and random terms
- Model notation
- Variance decomposition

Part 2: Applications

- Selection models
- Practical examples
- Variance components
- Ridges and Kernels

Part 1 - Concepts

History of mixed models

Francis Galton - 1886: Regression and heritability

Ronald Fisher - 1918: Infinitesimal model (**P = G + E**)

Sewall Wright - 1922: Genetic relationship

Charles Henderson - 1950, 1968: BLUP using relationship

Mixed models in plant breeding

- *Heart and soul* of plant breeding (Xavier et al 2017)
- Variance components and heritability
- Trait associations (Gianola and Sorensen 2014)
- Estimation of genetic values (Piepho et al 2008)
- Estimation of breeding values
- Prediction of unphenotyped lines (de los Campos et al 2013)
- Selection index
- Genome-wide association analysis (Yang et al 2014)
- All sorts of inference (Robinson 1991)

Fixed and random terms

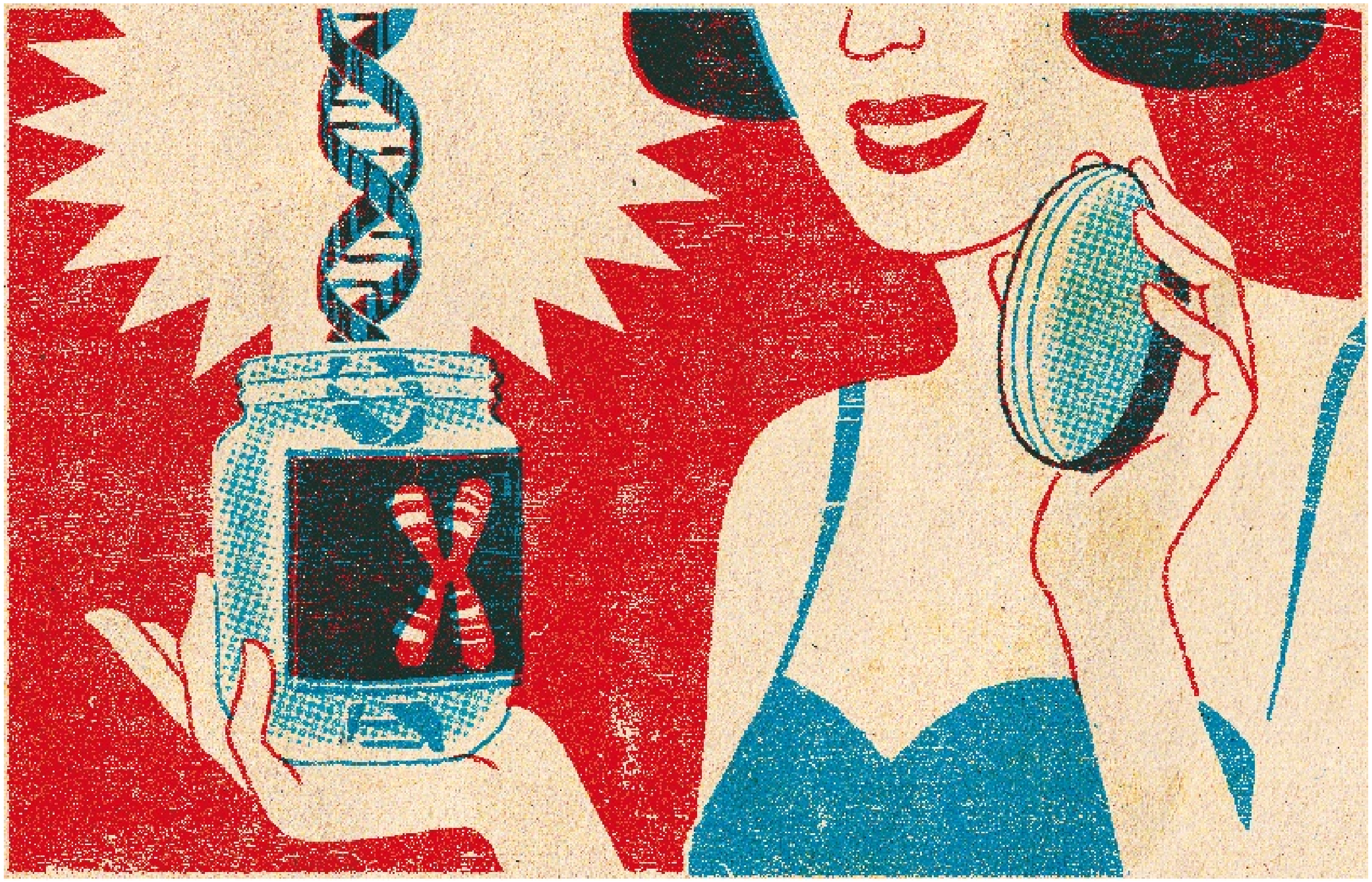
Fixed effect

- Assumed to be invariable (often you cannot recollect the data)
- Inferences are made upon the parameters
- Results can not be extrapolated to other datasets
- Example: Overall mean and environmental effects

Random effects

- You may not have all the levels available
- Inference are made on variance components
- Prior assumption: coefficients are normally distributed
- Results can not be extrapolated to other datasets
- Example: Genetic effects

Let's unleash the beast



Model notation

- Linear model: $y = Xb + Zu + e$
- With variance: $y \sim N(Xb, ZKZ\sigma^2_u + I\sigma^2_e)$

Assuming: $u \sim N(0, K\sigma^2_u)$ and $e \sim N(0, I\sigma^2_e)$

Henderson equation

$$\begin{bmatrix} X'X & Z'X \\ X'Z & Z'Z + \lambda K^{-1} \end{bmatrix} \begin{bmatrix} b \\ u \end{bmatrix} = \begin{bmatrix} X'y \\ Z'y \end{bmatrix}$$

Summary:

- We know (data): $x = \{y, X, Z, K\}$
- We want (parameters): $\theta = \{b, u, \sigma^2_a, \sigma^2_e\}$
- Estimation based on Gaussian likelihood: $L(x|\theta)$

Model notation

- **y** = vector of observations (*n*)
- **X** = design matrix of fixed effects (*n* x *p*)
- **Z** = design (or incidence) matrix of random effects (*n* x *p*)
- **K** = random effect correlation matrix (*q* x *q*)
- **u** = vector of random effect coefficients (*q*)
- **b** = vector of fixed effect coefficients (*p*)
- **e** = vector of residuals (*n*)
- σ_a^2 = marker effect variance (1)
- σ_u^2 = random effect variance (1)
- σ_e^2 = residual variance (1)
- $\lambda = \sigma_e^2 / \sigma_u^2$ (Regularization parameters) (1)

Model notation

The mixed model can also be notated as follows

$$y = Wg + e$$

Solved as

$$[W'W + \Sigma]g = [W'y]$$

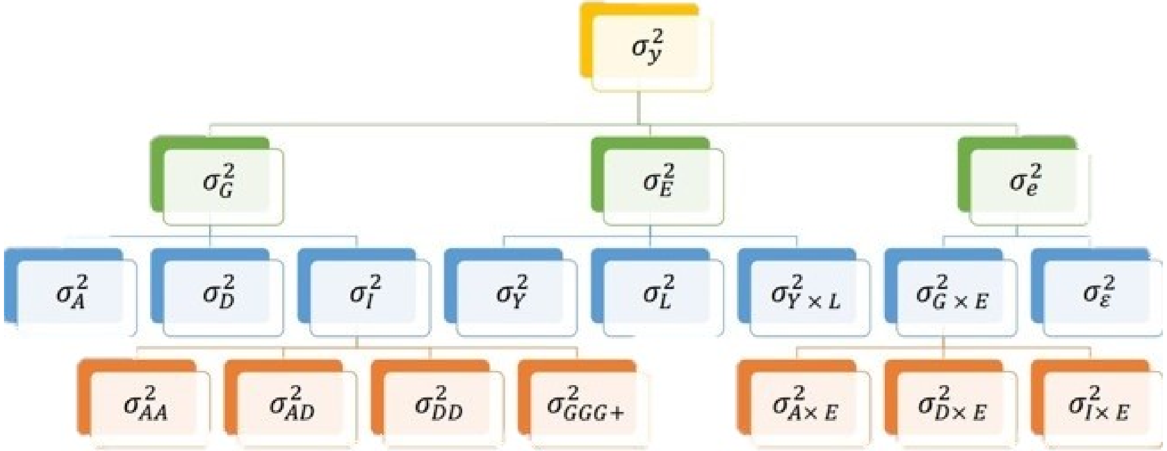
Where

$W = [X, Z]$

$g = [b, u]$

$\Sigma = \begin{bmatrix} 0 & 0 \\ 0 & \lambda K^{-1} \end{bmatrix}$

Variance decomposition



Part 2 - Applications

Selection

1 *Genetic values*

- BLUPs or BLUEs from replicated trials
- Captures additive and non-additive genetics together

2 *Breeding values*

- Use pedigree information to create K
- Captures additive genetics (heritable)
- Trials not necessarily replicated

3 *Genomic Breeding values*

- Genotypic information replaces pedigree
- Any signal: additivity, dominance and epistasis

Examples

- Example 1: Balanced data, no kinship
- Example 2: Balanced data, with kinship
- Example 3: Unbalanced data, with kinship
- Example 4: Balanced data, missing individual

Example 1

Data:

```
##    Env Gen Phe
## 1   E1  G1  47
## 2   E1  G2  51
## 3   E1  G3  46
## 4   E1  G4  58
## 5   E2  G1  52
## 6   E2  G2  46
## 7   E2  G3  52
## 8   E2  G4  54
## 9   E3  G1  53
## 10  E3  G2  48
## 11  E3  G3  58
## 12  E3  G4  52
```

Model: $Phenotype = Environment_{(F)} + Genotype_{(R)}$

Example 1

Design matrix W:

```
##    EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## 1      1     0     0     1     0     0     0
## 2      1     0     0     0     1     0     0
## 3      1     0     0     0     0     1     0
## 4      1     0     0     0     0     0     1
## 5      0     1     0     1     0     0     0
## 6      0     1     0     0     1     0     0
## 7      0     1     0     0     0     1     0
## 8      0     1     0     0     0     0     1
## 9      0     0     1     1     0     0     0
## 10     0     0     1     0     1     0     0
## 11     0     0     1     0     0     1     0
## 12     0     0     1     0     0     0     1
```

Example 1

$W'W$:

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     4     0     0     1     1     1     1
## EnvE2     0     4     0     1     1     1     1
## EnvE3     0     0     4     1     1     1     1
## GenG1     1     1     1     3     0     0     0
## GenG2     1     1     1     0     3     0     0
## GenG3     1     1     1     0     0     3     0
## GenG4     1     1     1     0     0     0     3
```

Example 1

Left-hand side ($W'W + \Sigma$):

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     4     0     0  1.00  1.00  1.00  1.00
## EnvE2     0     4     0  1.00  1.00  1.00  1.00
## EnvE3     0     0     4  1.00  1.00  1.00  1.00
## GenG1     1     1     1  3.17  0.00  0.00  0.00
## GenG2     1     1     1  0.00  3.17  0.00  0.00
## GenG3     1     1     1  0.00  0.00  3.17  0.00
## GenG4     1     1     1  0.00  0.00  0.00  3.17
```

Assuming independent individuals: $K = I$

Regularization: $\lambda = \sigma_e^2/\sigma_u^2 = 1.64/9.56 = 0.17$

Example 1

Right-hand side ($W'y$):

```
##       [,1]
## EnvE1  202
## EnvE2  204
## EnvE3  211
## GenG1  152
## GenG2  145
## GenG3  156
## GenG4  164
```

Example 1

We can find coefficients through least-square solution

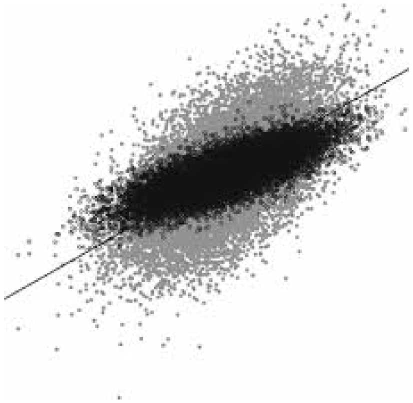
$$g = (LHS)^{-1}(RHS) = (W'W + \Sigma)^{-1}W'y$$

```
##        [,1]
## EnvE1 50.50
## EnvE2 51.00
## EnvE3 52.75
## GenG1 -0.71
## GenG2 -2.92
## GenG3  0.55
## GenG4  3.08
```

Shrinkage

$BLUE = \frac{w' y}{w' w} = \frac{sum}{n}$ = *simple average*

$BLUP = \frac{w' y}{w' w + \lambda} = \frac{sum}{n + \lambda}$ = *biased average* = $BLUE \times h^2$



Note:

- More observations = less shrinkage
- Higher heritability = less shrinkage: $\lambda = \frac{h^2 - 1}{h^2}$

Example 2

If we know the relationship among individuals:

```
##       GenG1 GenG2 GenG3 GenG4
## GenG1  1.00  0.64  0.23  0.48
## GenG2  0.64  1.00  0.33  0.67
## GenG3  0.23  0.33  1.00  0.31
## GenG4  0.48  0.67  0.31  1.00
```

Example 2

Then we estimate λK^{-1}

```
##       GenG1 GenG2 GenG3 GenG4
## GenG1  0.15 -0.09  0.00 -0.01
## GenG2 -0.09  0.22 -0.02 -0.10
## GenG3  0.00 -0.02  0.10 -0.02
## GenG4 -0.01 -0.10 -0.02  0.17
```

Regularization: $\lambda = \sigma_e^2/\sigma_u^2 = 1.64/17.70 = 0.09$

Example 2

And the left-hand side becomes

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     4     0     0  1.00  1.00  1.00  1.00
## EnvE2     0     4     0  1.00  1.00  1.00  1.00
## EnvE3     0     0     4  1.00  1.00  1.00  1.00
## GenG1     1     1     1  3.15 -0.09  0.00 -0.01
## GenG2     1     1     1 -0.09  3.22 -0.02 -0.10
## GenG3     1     1     1  0.00 -0.02  3.10 -0.02
## GenG4     1     1     1 -0.01 -0.10 -0.02  3.17
```

Example 2

We can find coefficients through least-square solution

$$g = (LHS)^{-1}(RHS) = (W'W + \Sigma)^{-1}W'y$$

```
##        [,1]
## EnvE1 51.05
## EnvE2 51.55
## EnvE3 53.30
## GenG1 -1.32
## GenG2 -3.34
## GenG3  0.03
## GenG4  2.45
```

Genetic coefficients shrink more: Var(A) < Var(G)

Example 3

What if we have missing data?

```
##    Env Gen Phe
## 1   E1  G1  47
## 2   E1  G2  51
## 3   E1  G3  NA
## 4   E1  G4  58
## 5   E2  G1  52
## 6   E2  G2  46
## 7   E2  G3  52
## 8   E2  G4  NA
## 9   E3  G1  53
## 10  E3  G2  48
## 11  E3  G3  58
## 12  E3  G4  52
```

Example 3

Rows of missing points are removed

```
##    EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## 1      1     0     0     1     0     0     0
## 2      1     0     0     0     1     0     0
## 4      1     0     0     0     0     0     1
## 5      0     1     0     1     0     0     0
## 6      0     1     0     0     1     0     0
## 7      0     1     0     0     0     1     0
## 9      0     0     1     1     0     0     0
## 10     0     0     1     0     1     0     0
## 11     0     0     1     0     0     1     0
## 12     0     0     1     0     0     0     1
```

Example 3

$W'W$:

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     3     0     0     1     1     0     1
## EnvE2     0     3     0     1     1     1     0
## EnvE3     0     0     4     1     1     1     1
## GenG1     1     1     1     3     0     0     0
## GenG2     1     1     1     0     3     0     0
## GenG3     0     1     1     0     0     2     0
## GenG4     1     0     1     0     0     0     2
```

Example 3

Left-hand side ($W'W + \Sigma$):

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     3     0     0  1.00  1.00  0.00  1.00
## EnvE2     0     3     0  1.00  1.00  1.00  0.00
## EnvE3     0     0     4  1.00  1.00  1.00  1.00
## GenG1     1     1     1  3.10 -0.06  0.00 -0.01
## GenG2     1     1     1 -0.06  3.15 -0.01 -0.07
## GenG3     0     1     1  0.00 -0.01  2.07 -0.01
## GenG4     1     0     1 -0.01 -0.07 -0.01  2.11
```

Regularization: $\lambda = \sigma^2_e/\sigma^2_u = 1.21/19.61 = 0.06$

Example 3

Right-hand side ($W'y$):

```
##        [,1]
## EnvE1  156
## EnvE2  150
## EnvE3  211
## GenG1  152
## GenG2  145
## GenG3  110
## GenG4  110
```

Example 3

Find coefficients through least-square solution

$$g = (LHS)^{-1}(RHS) = (W'W + \Sigma)^{-1}W'y$$

```
##        [,1]
## EnvE1 54.14
## EnvE2 51.70
## EnvE3 53.82
## GenG1 -2.56
## GenG2 -4.68
## GenG3  2.15
## GenG4  0.81
```

Example 4

What if we are missing data from a individual?

```
##    Env Gen Phe
## 1   E1  G1  NA
## 2   E1  G2  51
## 3   E1  G3  46
## 4   E1  G4  58
## 5   E2  G1  NA
## 6   E2  G2  46
## 7   E2  G3  52
## 8   E2  G4  54
## 9   E3  G1  NA
## 10  E3  G2  48
## 11  E3  G3  58
## 12  E3  G4  52
```

Example 4

Rows of missing points are removed

```
##    EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## 2      1     0     0     0     1     0     0
## 3      1     0     0     0     0     1     0
## 4      1     0     0     0     0     0     1
## 6      0     1     0     0     1     0     0
## 7      0     1     0     0     0     1     0
## 8      0     1     0     0     0     0     1
## 10     0     0     1     0     1     0     0
## 11     0     0     1     0     0     1     0
## 12     0     0     1     0     0     0     1
```

Example 4

$W'W$:

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     3     0     0     0     1     1     1
## EnvE2     0     3     0     0     1     1     1
## EnvE3     0     0     3     0     1     1     1
## GenG1     0     0     0     0     0     0     0
## GenG2     1     1     1     0     3     0     0
## GenG3     1     1     1     0     0     3     0
## GenG4     1     1     1     0     0     0     3
```

Example 4

Left-hand side ($W'W + \Sigma$):

```
##       EnvE1 EnvE2 EnvE3 GenG1 GenG2 GenG3 GenG4
## EnvE1     3     0     0  0.00  1.00  1.00  1.00
## EnvE2     0     3     0  0.00  1.00  1.00  1.00
## EnvE3     0     0     3  0.00  1.00  1.00  1.00
## GenG1     0     0     0  0.14 -0.08  0.00 -0.01
## GenG2     1     1     1 -0.08  3.19 -0.02 -0.09
## GenG3     1     1     1  0.00 -0.02  3.09 -0.01
## GenG4     1     1     1 -0.01 -0.09 -0.01  3.15
```

Regularization: $\lambda = \sigma_e^2 / \sigma_u^2 = 1.79/22.78 = 0.08$

Example 4

Right-hand side ($W'y$):

```
##       [,1]
## EnvE1  155
## EnvE2  152
## EnvE3  158
## GenG1    0
## GenG2  145
## GenG3  156
## GenG4  164
```

Example 4

Find coefficients through least-square solution

$$g = (LHS)^{-1}(RHS) = (W'W + \Sigma)^{-1}W'y$$

```
##        [,1]
## EnvE1 52.06
## EnvE2 51.06
## EnvE3 53.06
## GenG1 -1.82
## GenG2 -3.48
## GenG3 -0.07
## GenG4  2.38
```

Variance components

Expectation-Maximization REML (1977)

$\sigma_u^2 = \frac{u'K^{-1}u}{q - \lambda tr(K^{-1}C^{22})}$ and $\sigma_e^2 = \frac{e'y}{n-p}$

Bayesian Gibbs Sampling (1993)

$\sigma_u^2 = \frac{u'K^{-1}u + S_u\nu_u}{\chi^2(q+\nu_u)}$ and $\sigma_e^2 = \frac{e'e + S_e\nu_e}{\chi^2(n+\nu_e)}$

Predicted Residual Error Sum of Squares (PRESS) (2017)

- $\lambda = argmin(\sum e_i^2/(1-h_{ii})^2)$
- Where $H = (I + K\lambda)^{-1}$ and $e = y - \mu - Hy$

Ridges and Kernels

Kernel methods:

- Genetic signal is captured by the relationship matrix K
- Random effect coefficients are the **breeding values** (BV)
- Efficient to compute BV when $markers \gg individuals$
- Easy use and combine pedigree, markers and interactions

Ridge methods:

- Genetic signal is captured by the design matrix M
- Random effect coefficients are the **marker effects**
- Easy way to make predictions of unobserved individuals
- Enables to visualize where the QTLs are in the genome

Ridges and Kernels

Kernel

$$y = Xb + Zu + e, u \sim N(0, K\sigma_u^2)$$

Ridge

$$y = Xb + Ma + e, a \sim N(0, I\sigma_a^2)$$

Where

- M is the genotypic matrix, $m_{ij} = \{0, 1, 2\}$
- $K = \alpha MM'$
- $u = Ma$
- $\sigma_a^2 = \alpha\sigma_u^2$

Ridges and Kernels

Kernel model

$$\begin{bmatrix} X'X & Z'X \\ X'Z & Z'Z + K^{-1}(\sigma_e^2/\sigma_u^2) \end{bmatrix} \begin{bmatrix} b \\ u \end{bmatrix} = \begin{bmatrix} X'y \\ Z'y \end{bmatrix}$$

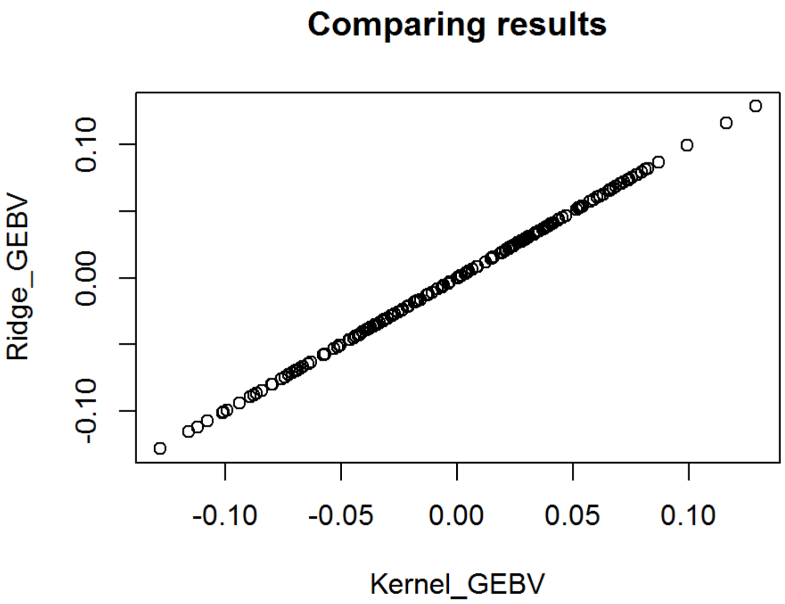
Ridge model

$$\begin{bmatrix} X'X & M'X \\ X'M & M'M + I^{-1}(\sigma_e^2/\sigma_a^2) \end{bmatrix} \begin{bmatrix} b \\ a \end{bmatrix} = \begin{bmatrix} X'y \\ M'y \end{bmatrix}$$

Both models capture same genetic signal (de los Campos 2015)

Ridges and Kernels

```
K = tcrossprod(M)/ncol(M)
GBLUP = reml(y=y,K=K); Kernel_GEBV = GBLUP$EBV
RRBLUP = reml(y=y,Z=M); Ridge_GEBV = M%*%RRBLUP$EBV
plot(Kernel_GEBV,Ridge_GEBV, main='Comparing results')
```



Break