

Genome-wide scan for linear mixed models

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1 Least squares

We apply the method of least squares to estimate the fixed-effect sizes.

1.1 Single block

Let

$$\mathbf{y} \sim \mathcal{N}(\mathbf{F}\boldsymbol{\alpha}; \mathbf{K}) \quad (1)$$

be the marginal likelihood of a LMM with a single covariate block \mathbf{F} . The maximum likelihood estimation of the fixed effects is

$$\hat{\boldsymbol{\alpha}} = (\mathbf{F}^\top \mathbf{K}^\dagger \mathbf{F})^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y}.$$

$$(\mathbf{X}^\top \mathbf{X})^\dagger = \begin{bmatrix} (\mathbf{L}^\top \mathbf{L})^\dagger + (\mathbf{L}^\top \mathbf{L})^\dagger (\mathbf{L}^\top \mathbf{R}) \mathbf{W}^\dagger (\mathbf{L}^\top \mathbf{R})^\top (\mathbf{L}^\top \mathbf{L})^\dagger & -(\mathbf{L}^\top \mathbf{L})^\dagger (\mathbf{L}^\top \mathbf{R}) \mathbf{W}^\dagger \\ -\mathbf{W}^\dagger (\mathbf{L}^\top \mathbf{R})^\top (\mathbf{L}^\top \mathbf{L})^\dagger & \mathbf{W}^\dagger \end{bmatrix},$$

from Eq. 3 of [1], where $\mathbf{W} = \mathbf{R}^\top \mathbf{R} - \mathbf{R}^\top \mathbf{L} (\mathbf{L}^\top \mathbf{L})^\dagger \mathbf{L}^\top \mathbf{R}$.

Defining $\mathbf{A} = \mathbf{L}^\top \mathbf{L}$ and $\mathbf{B} = \mathbf{L}^\top \mathbf{R}$ leads us to

$$(\mathbf{X}^\top \mathbf{X})^\dagger \mathbf{X}^\top = \begin{bmatrix} \mathbf{A}^\dagger \mathbf{L}^\top + \mathbf{A}^\dagger \mathbf{B} \mathbf{W}^\dagger \mathbf{B}^\top \mathbf{A}^\dagger \mathbf{L}^\top - \mathbf{A}^\dagger \mathbf{B} \mathbf{W}^\dagger \mathbf{R}^\top \\ -\mathbf{W}^\dagger \mathbf{B}^\top \mathbf{A}^\dagger \mathbf{L}^\top + \mathbf{W}^\dagger \mathbf{R}^\top \end{bmatrix}.$$

Finally,

$$(\mathbf{X}^\top \mathbf{X})^\dagger \mathbf{X}^\top \mathbf{K}^{\frac{1}{2}\dagger} \mathbf{y} = \begin{bmatrix} \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} + \mathbf{A}^\dagger \mathbf{B} \mathbf{W}^\dagger \mathbf{B}^\top \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{A}^\dagger \mathbf{B} \mathbf{W}^\dagger \mathbf{G}^\top \mathbf{K}^\dagger \mathbf{y} \\ \mathbf{W}^\dagger \mathbf{G}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{W}^\dagger \mathbf{B}^\top \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} \end{bmatrix}.$$

A robust implementation of the above equation has to: (i) associate matrix multiplications in such a way that a sequence of $\mathbf{K}^\dagger \dots \mathbf{K}^\dagger$ is avoided; and (ii) handle low-rank matrices \mathbf{W} . A better association of matrix multiplications is given by

$$(\mathbf{X}^\top \mathbf{X})^\dagger \mathbf{X}^\top \mathbf{K}^{\frac{1}{2}\dagger} \mathbf{y} = \begin{bmatrix} \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} + \mathbf{A}^\dagger \mathbf{B} \mathbf{W}^\dagger (\mathbf{B}^\top \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{G}^\top \mathbf{K}^\dagger \mathbf{y}) \\ \mathbf{W}^\dagger (\mathbf{G}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{B}^\top \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y}) \end{bmatrix}.$$

\mathbf{W}^\dagger can be found via economic SVD decomposition.

1.3 Batch scan

Given a $n \times p$ covariate block \mathbf{G} , we want to quickly infer the maximum likelihood estimations of $\boldsymbol{\alpha}_i$ and β_i , for $i \in \{1, \dots, p\}$ denoting the \mathbf{G} columns. We define a diagonal matrix

$$\mathbf{W} = \text{dotd}(\mathbf{G}^\top, \mathbf{K}^\dagger \mathbf{G}) - \text{dotd}(\mathbf{G}^\top, \mathbf{K}^\dagger \mathbf{F} (\mathbf{L}^\top \mathbf{L})^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{G}),$$

where $\text{dotd}(\cdot, \cdot)$ is a function that returns the diagonal elements of a matrix multiplication with asymptotically lower computational cost and memory use.

Clearly,

$$\hat{\boldsymbol{\beta}} = \begin{bmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \\ \vdots \\ \hat{\beta}_p \end{bmatrix} = \mathbf{W}^\dagger (\mathbf{G}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{B}^\top \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y}).$$

We know that

$$\hat{\boldsymbol{\alpha}}_i = \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger (\mathbf{y} + (\mathbf{G}_i \mathbf{W}_i \mathbf{G}_i^\top) (\mathbf{K}^\dagger \mathbf{F} \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{K}^\dagger \mathbf{y})),$$

where \mathbf{G}_i is the i -th column of \mathbf{G} . For one-shot computation we do

$$\hat{\boldsymbol{\alpha}} = \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \left(\mathbf{y} \oplus \mathbf{G}_i \otimes ((\mathbf{W}_i \mathbf{G}_i^\top) (\mathbf{K}^\dagger \mathbf{F} \mathbf{A}^\dagger \mathbf{F}^\top \mathbf{K}^\dagger \mathbf{y} - \mathbf{K}^\dagger \mathbf{y}))^\top \right),$$

In practice, the method of least squares can be used to solve the above equation without explicitly finding pseudoinverses.

1.2 Double block

Let

$$\mathbf{y} \sim \mathcal{N}(\mathbf{F}\boldsymbol{\alpha} + \mathbf{G}\boldsymbol{\beta}; \mathbf{K})$$

be the marginal likelihood of a LMM with two covariate blocks \mathbf{F} and \mathbf{G} . We want to solve

$$\begin{bmatrix} \hat{\boldsymbol{\alpha}} \\ \hat{\boldsymbol{\beta}} \end{bmatrix} = (\mathbf{X}^\top \mathbf{X})^\dagger \mathbf{X}^\top \mathbf{K}^{\frac{1}{2}\dagger} \mathbf{y}$$

for

$$\mathbf{L} = \mathbf{K}^{\frac{1}{2}\dagger} \mathbf{F}, \quad \mathbf{R} = \mathbf{K}^{\frac{1}{2}\dagger} \mathbf{G} \quad \text{and} \quad \mathbf{X} = \begin{bmatrix} \mathbf{L} & \mathbf{R} \end{bmatrix}.$$

We have

where \oplus and \otimes are element-wise summation and multiplication with broadcasting.

2 Marginal likelihood

Replace \mathbf{K} by $\sigma^2 \mathbf{K}$ in Eq. (1). Log of the marginal likelihood is given by

$$-\frac{1}{2} \left(\log(2\pi) - \log \det |\sigma^2 \mathbf{K}| - (\mathbf{y} - \mathbf{F}\boldsymbol{\beta})^\top (\sigma^2 \mathbf{K})^\dagger (\mathbf{y} - \mathbf{F}\boldsymbol{\beta}) \right).$$

The maximum likelihood estimation and the restricted likelihood estimation of σ^2 are give by

$$\hat{\sigma}^2 = \frac{(\mathbf{y} - \mathbf{F}\hat{\boldsymbol{\beta}})^\top \mathbf{K}^\dagger (\mathbf{y} - \mathbf{F}\hat{\boldsymbol{\beta}})}{k}$$

for $k = n$ and $k = n - p$, respectively.

References

- [1] Charles A Rohde. "Generalized inverses of partitioned matrices". In: *Journal of the Society for Industrial and Applied Mathematics* 13.4 (1965), pp. 1033–1035.