Genome-wide scan for linear mixed models

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1 Single block

Let

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

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

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

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

2 Double block

Let

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

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

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

for

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

We have

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

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

Defining $\mathrm{A} = \mathrm{L}^\intercal\mathrm{L}$ and $\mathrm{B} = \mathrm{L}^\intercal\mathrm{R}$ leads us to

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

Finally,

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

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

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

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

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.