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FaST linear mixed models for genome-wide association studies

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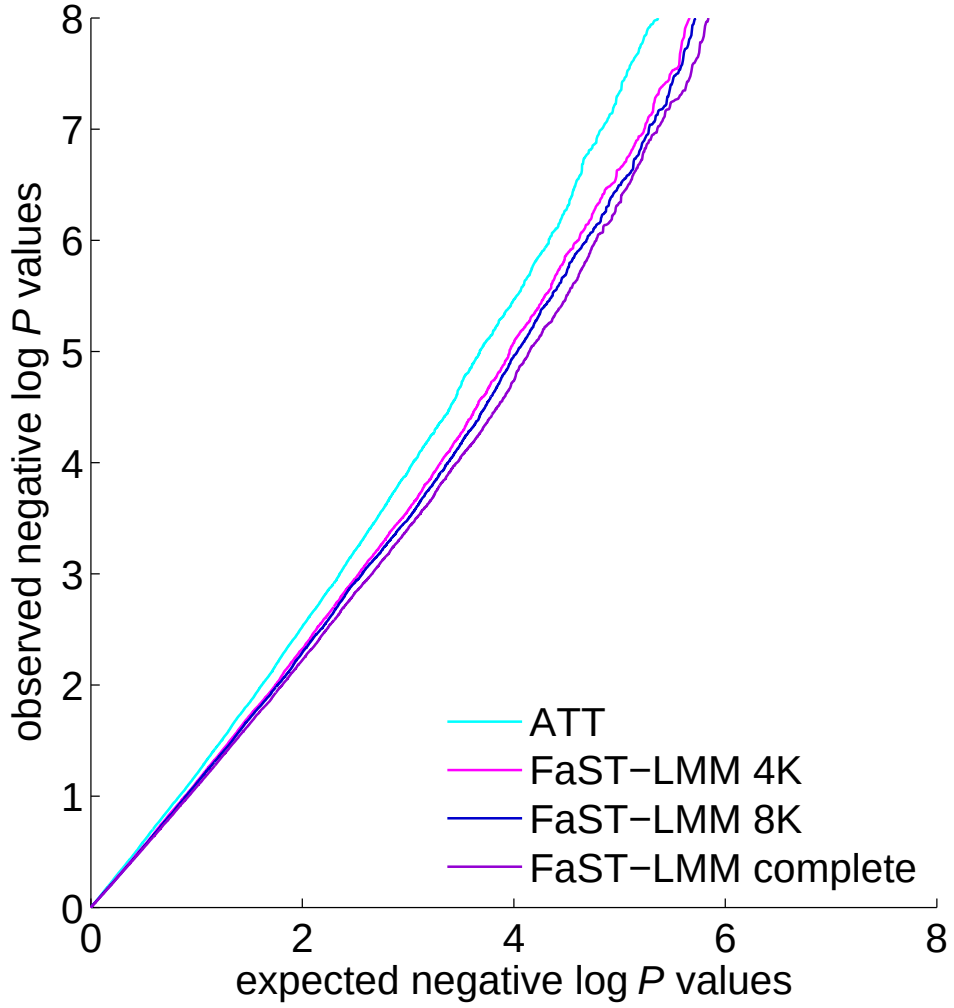
Supplementary Figure 1



Q-Q plots for the WTCCC data. Shown are observed versus expected negative log P values for the association analyses on the CD phenotype described in the main paper. We used FaST-LMM to test all SNPs on chromosome 1, and SNP sets of various sizes from all but this chromosome—the complete set (340K), 8K, and 4K—to compute the RRM. We also used ATT to compute P values.

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Supplementary Note 1: The FaST-LMM Algorithm

Here we describe our approach called FaST-LMM, which stands for *Fa*ctored *S*pectrally *T*ransformed *L*inear *M*ixed *M*odels. We derive formulas that allow for efficient evaluation of the likelihood as well as the maximum likelihood (ML) and restricted maximum likelihood (REML) parameters. We consider the cases where the genetic similarity matrix has full and low rank separately. The following notation will be used.

- n denotes the cohort size (the number of individuals represented in the data set).
- s denotes the total number of SNPs to be tested.
- d denotes the number of fixed effects in a single model, including the offset, the covariates, and in the case of an alternative model, the SNP to be tested. Although we use only one SNP at a time in our work, all equations follow regardless of the number of SNPs fixed effects.
- k denotes the rank of the genetic similarity matrix.
- s_c denotes the number of SNPs used to construct the genetic similarity matrix.
- $\mathbf{X} \in \mathbb{R}^{n \times d}$ denotes the matrix of fixed effects. This matrix includes the column of 1s corresponding to the offset, the covariates, and the SNP to be tested.
- $\mathbf{y} \in \mathbb{R}^{n \times 1}$ denotes the vector of phenotype measurements.
- $\mathbf{K} \in \mathbb{R}^{n \times n}$ denotes the symmetric positive (semi)-definite genetic similarity matrix.
- $\mathbf{I}_a$ denotes the identity matrix of dimension a. If no subscript a is given, the dimensionality is implied by the context.
- σ_g^2 denotes the magnitude of the genetic variance.
- σ_e^2 denotes the magnitude of the residual variance.
- $\delta \equiv \frac{\sigma_e^2}{\sigma_g^2}$ denotes the fraction of genetic variance and residual variance.
- $\boldsymbol{\beta} \in \mathbb{R}^{d \times 1}$ denotes the vector of fixed effect weights corresponding to $\mathbf{X} \in \mathbb{R}^{n \times d}$.
- $\mathbf{S} \in \mathbb{R}^{n \times n}$ denotes the diagonal matrix containing the eigenvalues of $\mathbf{K}$ ordered by their magnitude from large to small as diagonal elements.
- $\mathbf{U} \in \mathbb{R}^{n \times n}$ denotes to the matrix of eigenvectors of $\mathbf{K}$, in the order of the corresponding eigenvalues.
- $\mathbf{U}\mathbf{S}\mathbf{U}^\mathsf{T} = \mathbf{K}$ is the spectral decomposition of $\mathbf{K}$.
- $|\mathbf{A}|$ denotes the determinant of matrix $\mathbf{A}$.
- $\mathbf{A}^\mathsf{T}$ denotes the transpose of matrix $\mathbf{A}$.

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- $\mathbf{A}^{-1}$ denotes the inverse of matrix $\mathbf{A}$.
- $\mathbf{A}^{-\mathrm{T}}$ denotes the transposed inverse (or inverse of the transpose) of matrix $\mathbf{A}$.
- $[\mathbf{A}]_{ij}$ denotes the element of matrix $\mathbf{A}$ in the i^{th} row and j^{th} column.
- $[\mathbf{A}]_{i:}$ denotes the i^{th} row of matrix $\mathbf{A}$.
- $[\mathbf{a}]_i$ denotes the i^{th} entry of vector $\mathbf{a}$.
- $\mathbf{0}$ denotes a matrix where every entry is zero.
- $[\mathbf{A}, \mathbf{B}]$ denotes the concatenation of matrices $\mathbf{A}$ and $\mathbf{B}$.

1 LMMs with a full rank genetic similarity

We first consider the case where the genetic similarity matrix is of full rank (*i.e.*, the rank is equal to the cohort size).

1.1 Linear-time evaluation of the log likelihood

The log likelihood is parameterized by a weight vector $\boldsymbol{\beta}$ and the variances of the random components, σ_e^2 and σ_g^2:

$$LL\left(\sigma_e^2, \sigma_g^2, \boldsymbol{\beta}\right) = \log \mathcal{N}\left(\mathbf{y} | \mathbf{X}\boldsymbol{\beta}; \sigma_g^2 \mathbf{K} + \sigma_e^2 \mathbf{I}\right). \tag{1.1}$$

Introducing $\delta \equiv \frac{\sigma_e^2}{\sigma_g^2}$, the covariance matrix becomes $\sigma_g^2 (\mathbf{K} + \delta \mathbf{I})$, and the likelihood becomes a function of $\boldsymbol{\beta}$, δ and σ_g^2 [1]:

$$LL\left(\delta, \sigma_g^2, \boldsymbol{\beta}\right) = \log \mathcal{N}\left(\mathbf{y} | \mathbf{X}\boldsymbol{\beta}; \sigma_g^2 (\mathbf{K} + \delta \mathbf{I})\right).$$

Using the formula for the n-variate Normal distribution, we obtain

$$LL\left(\delta, \sigma_g^2, \boldsymbol{\beta}\right) = -\frac{1}{2}\left(n \log\left(2\pi\sigma_g^2\right) + \log\left(|(\mathbf{K} + \delta \mathbf{I})|\right) + \frac{1}{\sigma_g^2}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^{\mathrm{T}} (\mathbf{K} + \delta \mathbf{I})^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})\right). \tag{1.2}$$

Letting $\mathbf{U}\mathbf{S}\mathbf{U}^{\mathrm{T}} = \mathbf{K}$ be the spectral decomposition of $\mathbf{K}$, and noting that $\mathbf{I} = \mathbf{U}\mathbf{U}^{\mathrm{T}}$, Equation 1.2 becomes

$$LL\left(\delta, \sigma_g^2, \boldsymbol{\beta}\right) = -\frac{1}{2}\left(n \log\left(2\pi\sigma_g^2\right) + \log\left(\left|\left(\mathbf{U}\mathbf{S}\mathbf{U}^{\mathrm{T}} + \delta \mathbf{U}\mathbf{U}^{\mathrm{T}}\right)\right|\right) + \frac{1}{\sigma_g^2}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^{\mathrm{T}} \left(\mathbf{U}\mathbf{S}\mathbf{U}^{\mathrm{T}} + \delta \mathbf{U}\mathbf{U}^{\mathrm{T}}\right)^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})\right).$$

Next, we factor out $\mathbf{U}$ and $\mathbf{U}^{\mathrm{T}}$ from the covariance of the Normal, so that it becomes the diagonal matrix $(\mathbf{S} + \delta \mathbf{I})$, obtaining

$$-\frac{1}{2}\left(n \log\left(2\pi\sigma_g^2\right) + \log\left(\left|\mathbf{U}(\mathbf{S} + \delta \mathbf{I})\mathbf{U}^{\mathrm{T}}\right|\right) + \frac{1}{\sigma_g^2}(\mathbf{y} - \mathbf{X}\boldsymbol{\beta})^{\mathrm{T}} \left(\mathbf{U}(\mathbf{S} + \delta \mathbf{I})\mathbf{U}^{\mathrm{T}}\right)^{-1} (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})\right). \tag{1.3}$$

The determinant of the genetic similarity matrix, $|\mathbf{U}(\mathbf{S} + \delta \mathbf{I})\mathbf{U}^{\mathrm{T}}|$ can be written as $|(\mathbf{S} + \delta \mathbf{I})|$ using the properties that $|\mathbf{A}\mathbf{B}| = |\mathbf{A}||\mathbf{B}|$, and that $|\mathbf{U}| = |\mathbf{U}^{\mathrm{T}}| = 1$. The inverse of the genetic similarity

matrix can be rewritten as $\mathbf{U}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\mathbf{U}^{\mathsf{T}}$ using the properties that $(\mathbf{AB})^{-1}=\mathbf{B}^{-1}\mathbf{A}^{-1}$, that $\mathbf{U}^{-1}=\mathbf{U}^{\mathsf{T}}$, and that $\mathbf{U}^{-\mathsf{T}}=\mathbf{U}$. Thus, after additionally moving out $\mathbf{U}$ from the covariance term so that it now acts as a rotation matrix on the inputs ($\mathbf{X}$) and targets ($\mathbf{y}$), we obtain

$$-\frac{1}{2}\left(n\log\left(2\pi\sigma_g^2\right)+\log\left(\left|\mathbf{U}\right|\left|\left(\mathbf{S}+\delta\mathbf{I}\right)\right|\left|\mathbf{U}^{\mathsf{T}}\right|\right)+\frac{1}{\sigma_g^2}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)^{\mathsf{T}}\mathbf{U}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\mathbf{U}^{\mathsf{T}}\left(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}\right)\right)$$

$$=-\frac{1}{2}\left(n\log\left(2\pi\sigma_g^2\right)+\log\left(\left|\left(\mathbf{S}+\delta\mathbf{I}\right)\right|\right)+\frac{1}{\sigma_g^2}\left(\left(\mathbf{U}^{\mathsf{T}}\mathbf{y}\right)-\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)\boldsymbol{\beta}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\left(\mathbf{U}^{\mathsf{T}}\mathbf{y}\right)-\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)\boldsymbol{\beta}\right)\right). \tag{1.4}$$

The "Fa" in FaST-LMM gets its name from these factorizations. As the covariance matrix of the Normal distribution is now a diagonal matrix ($\mathbf{S}+\delta\mathbf{I}$), the log likelihood can be rewritten as the sum over n terms, yielding

$$-\frac{1}{2}\left(n\log\left(2\pi\sigma_g^2\right)+\sum_{i=1}^{n}\log\left(\left[\mathbf{S}\right]_{ii}+\delta\right)+\frac{1}{\sigma_g^2}\sum_{i=1}^{n}\frac{\left(\left[\mathbf{U}^{\mathsf{T}}\mathbf{y}\right]_i-\left[\mathbf{U}^{\mathsf{T}}\mathbf{X}\right]_{i:}\boldsymbol{\beta}\right)^2}{\left[\mathbf{S}\right]_{ii}+\delta}\right). \tag{1.5}$$

Note that this expression is equal to the product of n single-variate Normal distributions, on the data transformed by $\mathbf{U}^{\mathsf{T}}$, yielding the equation

$$LL\left(\delta,\sigma_g^2,\boldsymbol{\beta}\right)=\log\prod_{i=1}^{n}\mathcal{N}\left(\left[\mathbf{U}^{\mathsf{T}}\mathbf{y}\right]_i\middle|\left[\mathbf{U}^{\mathsf{T}}\mathbf{X}\right]_{i:}\boldsymbol{\beta};\sigma_g^2(\left[\mathbf{S}\right]_{ii}+\delta)\right).$$

Having pre-computed the spectral decomposition of $\mathbf{K}$, we can rotate the phenotype and all SNPs once to get $\mathbf{UX}$ and $\mathbf{Uy}$. Given the parameters δ,σ_g^2 and $\boldsymbol{\beta}$ each evaluation of the likelihood is now linear in the cohort size n, as compared to cubic for direct evaluation of Equation 1.1.

1.2 Finding the maximum likelihood fixed effect weights efficiently

We take the gradient of the log likelihood in Equation 1.4 with respect to $\boldsymbol{\beta}$ and set it to zero, giving

$$\mathbf{0}=\frac{1}{\sigma_g^2}\Big(\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{y}\right)-\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)\hat{\boldsymbol{\beta}}\Big).$$

Multiplying both sides by σ_g^2 and then bringing the part involving $\hat{\boldsymbol{\beta}}$ to one side, we get

$$\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)\hat{\boldsymbol{\beta}}=\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{y}\right).$$

Multiplying both sides by the inverse of the factor on the left side, we obtain

$$\hat{\boldsymbol{\beta}}=\left[\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)\right]^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}}\left(\mathbf{S}+\delta\mathbf{I}\right)^{-1}\left(\mathbf{U}^{\mathsf{T}}\mathbf{y}\right).$$

As $(\mathbf{S}+\delta\mathbf{I})$ is a diagonal matrix, the matrix products again can be written as a sum over n independent terms, yielding

$$\hat{\boldsymbol{\beta}}=\left[\sum_{i=1}^{n}\frac{1}{\left[\mathbf{S}\right]_{ii}+\delta}\left[\mathbf{U}^{\mathsf{T}}\mathbf{X}\right]_{i:}^{\mathsf{T}}\left[\mathbf{U}^{\mathsf{T}}\mathbf{X}\right]_{i:}\right]^{-1}\left[\sum_{i=1}^{n}\frac{1}{\left[\mathbf{S}\right]_{ii}+\delta}\left[\mathbf{U}^{\mathsf{T}}\mathbf{X}\right]_{i:}^{\mathsf{T}}\left[\mathbf{U}^{\mathsf{T}}\mathbf{y}\right]_i\right],$$

analogous to linear regression estimates for $\hat{\boldsymbol{\beta}}$ on the rotated data. Assuming that all the terms involving the spectral decomposition of $\mathbf{K}$ are precomputed, this equation can be evaluated in $O(n)$.

1.3 Finding the maximum likelihood genetic variance efficiently

We start by substituting $\hat{\boldsymbol{\beta}}$ from the previous section into the log likelihood, Equation 1.5, and set the derivative with respect to σ_g^2 to zero, giving

$$0 = -\frac{1}{2}\left(\frac{n}{\hat{\sigma}_g^2} - \frac{1}{\hat{\sigma}_g^4}\sum_{i=1}^{n}\frac{\left([\mathbf{U}^\mathrm{T}\mathbf{y}]_i - [\mathbf{U}^\mathrm{T}\mathbf{X}]_{i:}\hat{\boldsymbol{\beta}}\right)^2}{[\mathbf{S}]_{ii}+\delta}\right).$$

Multiplying both sides by $2\hat{\sigma}_g^4$ and solving for $\hat{\sigma}_g^2$, we get

$$\hat{\sigma}_g^2 = \frac{1}{n}\sum_{i=1}^{n}\frac{\left([\mathbf{U}^\mathrm{T}\mathbf{y}]_i - [\mathbf{U}^\mathrm{T}\mathbf{X}]_{i:}\hat{\boldsymbol{\beta}}\right)^2}{[\mathbf{S}]_{ii}+\delta}.$$

This equation also can be evaluated in $O(n)$.

1.4 Efficient evaluation of the maximum likelihood

Plugging in $\hat{\sigma}_g^2$ and $\hat{\boldsymbol{\beta}}$ into Equation 1.5, the log likelihood becomes a function only of δ, $LL(\delta, \hat{\sigma}_g^2(\delta), \hat{\boldsymbol{\beta}}(\delta)) = LL(\delta)$:

$$LL(\delta) = -\frac{1}{2}\left(n\log(2\pi) + \sum_{i=1}^{n}\log\left([\mathbf{S}]_{ii}+\delta\right) + n + n\log\frac{1}{n}\left(\sum_{i=1}^{n}\frac{\left([\mathbf{U}^\mathrm{T}\mathbf{y}]_i - [\mathbf{U}^\mathrm{T}\mathbf{X}]_{i:}\hat{\boldsymbol{\beta}}(\delta)\right)^2}{[\mathbf{S}]_{ii}+\delta}\right)\right).$$

As described next, we optimize this function of δ using a one-dimensional numerical optimizer to find the maximum likelihood value of δ, from which the maximum likelihood values of all the parameters can be directly computed.

1.5 Optimization of δ

As we've just shown, finding the maximum log likelihood of our model ($LL\left(\sigma_e^2, \sigma_g^2, \boldsymbol{\beta}\right)$) is equivalent to finding the value of δ that maximizes $LL(\delta)$, a non-convex optimization problem. To avoid local maxima in FaST-LMM, a quasi-exhaustive one dimensional optimization scheme similar to the one proposed in [1] is applied. In order to bracket local minima, we evaluate the maximum of the log likelihood for 100 equidistant values of $\log(\delta)$, ranging -10 to 10. Then, we apply Brent's method (a 1D numerical optimization algorithm) to find the locally optimal δ in each bracket where the middle log likelihood is higher than the log likelihoods of the neighboring evaluations.

To speed-up a full GWAS scan, one can find the maximum likelihood setting for δ for just the null-model, re-using the same δ for all alternative models. This speedup was described in [2] and is used in all of our experiments unless otherwise noted.

2 Relationship between spectral decomposition and singular value decomposition for the RRM and other factored genetic similarity matrices

Before we discuss the low-rank version of FaST-LMM, it will be useful to review the relationship between spectral decomposition and singular value decomposition (SVD) for matrices, for which the factorization $\mathbf{K} = \mathbf{W}\mathbf{W}^\mathsf{T}$ is known, such as the RRM or the Eigenstrat covariance matrix [3]. In this section, we shall refer to a matrix $\mathbf{K}$ that has this form as being *factored*.

The spectral decomposition of the genetic similarity matrix, $\mathbf{K}$, given by $\mathbf{U}\mathbf{S}\mathbf{U}^\mathsf{T} = \mathbf{K}$, yields the eigenvectors ($\mathbf{U}$) and eigenvalues ($\mathbf{S}$) of $\mathbf{K}$. In general, this decomposition can be determined by first computing the genetic similarity matrix ($\mathbf{K}$), and then taking the spectral decomposition of it. For many measures of genetic similarity, including RRM, the time complexity of computing $\mathbf{K}$ is $O(n^2 s_\mathrm{c})$, where s_c is the number of SNPs used to compute $\mathbf{K}$. Given the genetic similarity matrix, the eigenvalues and eigenvectors of $\mathbf{K}$ can then be found solving the spectral decomposition at a time complexity of $O(n^3)$ and space complexity of $O(n^2)$. If only the first k eigenvectors are desired, the computation can be achieved with other algorithms that have time complexity of $O(n^2 k)$ and a space complexity of $O(n^2)$.

When $\mathbf{K}$ if factored, however, one can bypass explicit computation of $\mathbf{K}$, obtaining the required eigenvectors and eigenvalues by direct application of an SVD to the $n \times s_\mathrm{c}$ data matrix of SNP markers at a time complexity of $O(n s_\mathrm{c}^2)$ (or $O(n s_\mathrm{c} k)$ for only the top k eigenvectors using, for example, [4]) and space complexity of $O(n s_\mathrm{c})$. Construction of $\mathbf{K}$ can be bypassed because (1) the eigenvectors (equivalently, singular vectors) of the factored matrix are the same as the singular vectors of the data matrix, and (2) the eigenvalues (equivalently singular values) of the factored matrix are the square of the singular values of the data matrix. This relationship is widely-known (*e.g.*, [5]) and is demonstrated below. In our experiments, FaST-LMM bypasses computation of the factored matrix to obtain the required spectral decomposition whenever $s_\mathrm{c} < n$.

Note that, when the rank of $\mathbf{K}$ is less than the cohort size n (such as occurs when the data matrix used to compute the factored genetic similarity matrix represents fewer SNPs than individuals), the SVD with time cost $O(n s_\mathrm{c}^2)$ is actually an *economy* SVD, that is, it yields only the first s_c eigenvectors. This set of eigenvectors is denoted $\mathbf{U}_1$ in Section 3 and referred to as the k-spectral decomposition in the main paper.

We now demonstrate the relationship just noted. Let $\mathbf{W} \in \mathbb{R}^{n \times s_\mathrm{c}}$ [6] be the matrix containing the set of SNPs used to compute the factored matrix, $\mathbf{K}$, defined as

$$\mathbf{K} \equiv \mathbf{W}\mathbf{W}^\mathsf{T}. \tag{2.1}$$

Let $\mathbf{U}\tilde{\mathbf{S}}\mathbf{V}^\mathsf{T}$ be the SVD of $\mathbf{W}$. Then Equation 2.1 can be rewritten as

$$\mathbf{K} = \left(\mathbf{U}\tilde{\mathbf{S}}\mathbf{V}^\mathsf{T}\right)\left(\mathbf{U}\tilde{\mathbf{S}}\mathbf{V}^\mathsf{T}\right)^\mathsf{T} = \mathbf{U}\tilde{\mathbf{S}}\mathbf{V}^\mathsf{T}\mathbf{V}\tilde{\mathbf{S}}\mathbf{U}^\mathsf{T}.$$

Because $\mathbf{V}^\mathsf{T}\mathbf{V} = \mathbf{I}$, we obtain

$$\mathbf{K} = \mathbf{U}\tilde{\mathbf{S}}\tilde{\mathbf{S}}\mathbf{U}^\mathsf{T} = \mathbf{U}\mathbf{S}\mathbf{U}^\mathsf{T},$$

where $\mathbf{S}_{ii} \equiv \tilde{\mathbf{S}}_{ii}\tilde{\mathbf{S}}_{ii}$. By definition, $\mathbf{U}$ consists of the eigenvectors of $\mathbf{K}$ (because it satisfies the properties of a spectral decomposition of $\mathbf{K}$, namely that $\mathbf{K} = \mathbf{USU}^\mathsf{T}$ where $\mathbf{S}$ is diagonal and $\mathbf{U}$ contains orthonormal vectors). Furthermore, the eigenvalues of $\mathbf{K}$ are given by $\tilde{\mathbf{S}}_{ii}^2$. Consequently, we can obtain the spectral decomposition of $\mathbf{K}$ by computing the SVD of $\mathbf{W}$, which has time cost $O(ns_c^2)$.

3 LMMs with a low rank genetic similarity matrix

Now we consider the evaluation of the likelihood when the rank of $\mathbf{K}$, k, is low ($k < n$) (*i.e.*, $\mathbf{K}$ is not full rank). This condition will occur when the RRM is used and the number of SNPs used to estimate it, $s_c = k$, is smaller than n. It will also occur if we reduce the rank of $\mathbf{K}$ to $k \leq \min(n, s_c)$ by eliminating the eigenvectors with the lowest eigenvalues as described in Discussion of the main paper. We address both possibilities in this section.

Let $\mathbf{USU}^\mathsf{T} = \mathbf{K}$ be the complete spectral decomposition of $\mathbf{K}$. Thus, $\mathbf{S}$ is an $n \times n$ diagonal matrix containing the k non-zero eigenvalues on the top-left of the diagonal, followed by $n-k$ zeros on the bottom-right, and $\mathbf{U}$ is an $n \times n$ matrix of eigenvectors. Now, write the full $n \times n$ orthonormal matrix $\mathbf{U}$ as $\mathbf{U} \equiv [\mathbf{U}_1, \mathbf{U}_2]$, where $\mathbf{U}_1 \in \mathbb{R}^{n \times k}$ contains the eigenvectors corresponding to non-zero eigenvalues, and $\mathbf{U}_2 \in \mathbb{R}^{n \times n-k}$ contains the eigenvectors corresponding to zero eigenvalues. Thus, we have

$$\mathbf{K} = \mathbf{USU}^\mathsf{T} = [\mathbf{U}_1, \mathbf{U}_2] \begin{bmatrix} \mathbf{S}_1 & \mathbf{0} \\ \mathbf{0} & \mathbf{S}_2 \end{bmatrix} [\mathbf{U}_1, \mathbf{U}_2]^\mathsf{T} = \mathbf{U}_1\mathbf{S}_1\mathbf{U}_1^\mathsf{T} + \mathbf{U}_2\mathbf{S}_2\mathbf{U}_2^\mathsf{T}.$$

As $\mathbf{S}_2 = [\mathbf{0}]$, $\mathbf{K}$ can be recovered by the k-spectral decomposition of $\mathbf{K}$:

$$\mathbf{K} = \mathbf{U}_1\mathbf{S}_1\mathbf{U}_1^\mathsf{T}.$$

The expression $(\mathbf{K} + \delta\mathbf{I})$, however, is always of full rank (because $\delta > 0$):

$$\mathbf{K} + \delta\mathbf{I} = \mathbf{U}\left(\mathbf{S} + \delta\mathbf{I}\right)\mathbf{U}^\mathsf{T} = \mathbf{U}\begin{bmatrix} \mathbf{S}_1 + \delta\mathbf{I}_k & \mathbf{0} \\ \mathbf{0} & \delta\mathbf{I}_{n-k} \end{bmatrix}\mathbf{U}^\mathsf{T}.$$

Therefore, it is not possible to simply ignore $\mathbf{U}_2$ while using our previous approach (as in in Section 1), as $\mathbf{U}_2$ enters the expression for the log likelihood. Furthermore, directly computing the complete spectral decomposition does not exploit the low rank of $\mathbf{K}$. Thus, we use algebraic manipulations to rewrite the likelihood in terms not involving $\mathbf{U}_2$, as explained next. As a result, we incur only the computational complexity of computing $\mathbf{U}_1$ rather than $\mathbf{U}$.

3.1 Linear time evaluation of the likelihood

To exploit the low rank of $\mathbf{K}$ to evaluate the log likelihood efficiently, one possible approach would be to augment the spectrum using $n-k$ vectors that are orthogonal to the first k. Unfortunately, this strategy has a time complexity of $O((n-k)n^2)$. Consequently, we take the following alternative approach.

We begin with Equation 1.2:

$$LL(\delta, \sigma_g^2, \boldsymbol{\beta}) = -\frac{1}{2}\left(n \log\left(2\pi\sigma_g^2\right) + \log\left|(\mathbf{K}+\delta\mathbf{I})\right| + \frac{1}{\sigma_g^2}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta})^{\mathsf{T}}(\mathbf{K}+\delta\mathbf{I})^{-1}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta})\right).$$

The two terms involving $\mathbf{K}+\delta\mathbf{I}$ are highlighted in color and will be treated separately in the following.

As in Equation 1.5, the log-determinant of the genetic similarity matrix can be efficiently computed using the economy SVD of $\mathbf{X}$ to obtain the spectral decomposition of $\mathbf{K}$:

$$\log\left|(\mathbf{K}+\delta\mathbf{I})\right| = \sum_{i=1}^{n}\log\left([\mathbf{S}]_{ii}+\delta\right) = \sum_{i=1}^{k}\log\left([\mathbf{S}]_{ii}+\delta\right) + (n-k)\left(\log\delta\right), \tag{3.1}$$

where we use the fact that the last $n-k$ singular values are zero.

Also, as we show in Section 3.3, the residual quadratic form can be evaluated using the low-rank decomposition:

$$\begin{aligned}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta})^{\mathsf{T}}(\mathbf{K}+\delta\mathbf{I})^{-1}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}) &= \left(\mathbf{U}_1^{\mathsf{T}}\mathbf{y}-\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\boldsymbol{\beta}\right)^{\mathsf{T}}\left(\mathbf{S}_1+\delta\mathbf{I}_k\right)^{-1}\left(\mathbf{U}_1^{\mathsf{T}}\mathbf{y}-\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\boldsymbol{\beta}\right)\\ &+\frac{1}{\delta}\left(\left(\mathbf{I}_n-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{y}-\left(\mathbf{I}_n-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{X}\boldsymbol{\beta}\right)^{\mathsf{T}}\left(\left(\mathbf{I}_n-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{y}-\left(\mathbf{I}_n-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{X}\boldsymbol{\beta}\right).\end{aligned} \tag{3.2}$$

Furthermore, both terms in the expression on the right can be written as sums, leading to

$$\begin{aligned}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta})^{\mathsf{T}}(\mathbf{K}+\delta\mathbf{I})^{-1}(\mathbf{y}-\mathbf{X}\boldsymbol{\beta}) &= \sum_{i=1}^{k}\frac{\left([\mathbf{U}_1^{\mathsf{T}}\mathbf{y}]_i-[\mathbf{U}_1^{\mathsf{T}}\mathbf{X}]_{i:}\boldsymbol{\beta}\right)^2}{[\mathbf{S}]_{ii}+\delta} +\\ &\frac{1}{\delta}\sum_{i=1}^{n}\left(\left[\mathbf{y}-\mathbf{U}_1\left(\mathbf{U}_1^{\mathsf{T}}\mathbf{y}\right)\right]_i-\left[\mathbf{X}-\mathbf{U}_1\left(\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\right)\right]_i\boldsymbol{\beta}\right)^2.\end{aligned} \tag{3.3}$$

3.2 Finding the maximum likelihood and parameters efficiently

Plugging both the determinant (Equation 3.1) and the quadratic form (Equation 3.3) into the log likelihood, we obtain

$$\begin{aligned}LL(\delta, \sigma_g^2, \boldsymbol{\beta}) = &-\frac{1}{2}\left(n\log\left(2\pi\sigma_g^2\right)+\sum_{i=1}^{k}\log\left([\mathbf{S}]_{ii}+\delta\right)+(n-k)\left(\log\delta\right)\right)\\ &-\frac{1}{2\sigma_g^2}\left(\sum_{i=1}^{k}\frac{\left([\mathbf{U}_1^{\mathsf{T}}\mathbf{y}]_i-[\mathbf{U}_1^{\mathsf{T}}\mathbf{X}]_{i:}\boldsymbol{\beta}\right)^2}{[\mathbf{S}]_{ii}+\delta}+\frac{1}{\delta}\sum_{i=1}^{n}\left(\left[\mathbf{y}-\mathbf{U}_1\left(\mathbf{U}_1^{\mathsf{T}}\mathbf{y}\right)\right]_i-\left[\mathbf{X}-\mathbf{U}_1\left(\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\right)\right]_i\boldsymbol{\beta}\right)^2\right).\end{aligned} \tag{3.4}$$

Setting the gradient of $LL(\delta, \sigma_g^2, \boldsymbol{\beta})$ in Equation 3.4 with respect to $\boldsymbol{\beta}$ to zero, we obtain

$$\begin{aligned}\hat{\boldsymbol{\beta}} = &\left[\left(\sum_{i=1}^{k}\frac{1}{[\mathbf{S}]_{ii}+\delta}\left[\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\right]_{i:}^{\mathsf{T}}\left[\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\right]_{i:}\right)+\left(\frac{1}{\delta}\sum_{i=1}^{n}\left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{X}\right]_{i:}^{\mathsf{T}}\left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{X}\right]_{i:}\right)\right]^{-1}\\ &*\left[\left(\sum_{i=1}^{k}\frac{1}{[\mathbf{S}]_{ii}+\delta}\left[\mathbf{U}_1^{\mathsf{T}}\mathbf{X}\right]_{i:}^{\mathsf{T}}\left[\mathbf{U}_1^{\mathsf{T}}\mathbf{y}\right]_{i}\right)+\left(\frac{1}{\delta}\sum_{i=1}^{n}\left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{X}\right]_{i:}^{\mathsf{T}}\left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{y}\right]_{i}\right)\right].\end{aligned} \tag{3.5}$$

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Plugging $\hat{\boldsymbol{\beta}}$ into the log likelihood and setting the derivative with respect to σ_g^2 to zero, we get

$$0 = -\frac{1}{2}\left(\frac{n}{\hat{\sigma}_g^2} - \frac{1}{\hat{\sigma}_g^4}\left(\sum_{i=1}^{k}\frac{\left(\left[\mathbf{U}_1^\mathsf{T}\mathbf{y}\right]_i - \left[\mathbf{U}_1^\mathsf{T}\mathbf{X}\right]_{i:}\hat{\boldsymbol{\beta}}\right)^2}{[\mathbf{S}]_{ii}+\delta} + \frac{1}{\delta}\sum_{i=1}^{n}\left(\left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^\mathsf{T}\right)\mathbf{y}\right]_i - \left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^\mathsf{T}\right)\mathbf{X}\right]_{i:}\hat{\boldsymbol{\beta}}\right)^2\right)\right).$$

Consequently,

$$\hat{\sigma}_g^2 = \frac{1}{n}\left(\sum_{i=1}^{k}\frac{\left(\left[\mathbf{U}_1^\mathsf{T}\mathbf{y}\right]_i - \left[\mathbf{U}_1^\mathsf{T}\mathbf{X}\right]_{i:}\hat{\boldsymbol{\beta}}\right)^2}{[\mathbf{S}]_{ii}+\delta} + \frac{1}{\delta}\sum_{i=1}^{n}\left(\left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^\mathsf{T}\right)\mathbf{y}\right]_i - \left[\left(\mathbf{I}-\mathbf{U}_1\mathbf{U}_1^\mathsf{T}\right)\mathbf{X}\right]_{i:}\hat{\boldsymbol{\beta}}\right)^2\right). \quad (3.6)$$

Plugging Equations 3.5 and 3.6 into 3.4 yields

$$\begin{aligned} LL(\delta,\hat{\sigma}_g^2,\hat{\boldsymbol{\beta}}) = &-\frac{1}{2}\left(n\log(2\pi) + \sum_{i=1}^{k}\log\left([\mathbf{S}]_{ii}+\delta\right) + (n-k)\left(\log\delta\right)\right) \\ &-\frac{1}{2}\left(n + n\log\frac{1}{n}\left(\sum_{i=1}^{k}\frac{\left(\left[\mathbf{U}_1^\mathsf{T}\mathbf{y}\right]_i - \left[\mathbf{U}_1^\mathsf{T}\mathbf{X}\right]_{i:}\hat{\boldsymbol{\beta}}\right)^2}{[\mathbf{S}]_{ii}+\delta} + \frac{1}{\delta}\sum_{i=1}^{n}\left(\left[\mathbf{y}-\mathbf{U}_1\left(\mathbf{U}_1^\mathsf{T}\mathbf{y}\right)\right]_i - \left[\mathbf{X}-\mathbf{U}_1\left(\mathbf{U}_1^\mathsf{T}\mathbf{X}\right)\right]_i\hat{\boldsymbol{\beta}}\right)^2\right)\right), \end{aligned} \quad (3.7)$$

which can be evaluated in $O(n+k)$.

3.3 Derivation of the low-rank quadratic form

Let $\mathbf{K}$ be a rank k genetic similarity matrix whose spectral decomposition can be written

$$\mathbf{K} = \mathbf{U}\mathbf{S}\mathbf{U}^\mathsf{T} = \mathbf{U}_1\mathbf{S}_1\mathbf{U}_1^\mathsf{T} + \mathbf{U}_2\mathbf{S}_2\mathbf{U}_2^\mathsf{T} = \mathbf{U}_1\mathbf{S}_1\mathbf{U}_1^\mathsf{T} + \mathbf{U}_2\left[\mathbf{0}\right]\mathbf{U}_2^\mathsf{T} = \mathbf{U}_1\mathbf{S}_1\mathbf{U}_1^\mathsf{T},$$

where

$$\mathbf{U} = \left[\mathbf{U}_1, \mathbf{U}_2\right], \quad (3.8)$$

$\mathbf{U}_1 \in \mathbb{R}^{n\times k}$ contains the eigenvectors corresponding to non-zero eigenvalues, and $\mathbf{U}_2 \in \mathbb{R}^{n\times n-k}$. Using the fact that $\mathbf{U} \in \mathbb{R}_{n\times n}$ is a normal matrix, that is, $\mathbf{U}^{-1} = \mathbf{U}^\mathsf{T}$, we have

$$\mathbf{I}_n = \mathbf{U}\mathbf{U}^\mathsf{T} = \left[\mathbf{U}_1, \mathbf{U}_2\right]\left[\mathbf{U}_1, \mathbf{U}_2\right]^\mathsf{T} = \mathbf{U}_1\mathbf{U}_1^\mathsf{T} + \mathbf{U}_2\mathbf{U}_2^\mathsf{T}. \quad (3.9)$$

Solving Equation 3.9 for $\mathbf{U}_2\mathbf{U}_2^\mathsf{T}$, we get

$$\mathbf{U}_2\mathbf{U}_2^\mathsf{T} = \mathbf{I}_n - \mathbf{U}_1\mathbf{U}_1^\mathsf{T}. \quad (3.10)$$

Further, because the columns of $\mathbf{U}$ are orthonormal, it follows that

$$\mathbf{I}_n = \mathbf{U}^\mathsf{T}\mathbf{U},$$

$$\mathbf{I}_k = \mathbf{U}_1^\mathsf{T}\mathbf{U}_1,$$

$$\mathbf{I}_{n-k} = \mathbf{U}_2^{\mathsf{T}}\mathbf{U}_2. \tag{3.11}$$

Let $\mathbf{a} \equiv (\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$. Our goal is to efficiently evaluate $\mathbf{a}^{\mathsf{T}} (\mathbf{K} + \delta\mathbf{I})^{-1} \mathbf{a}$. Substituting the spectral decomposition for $\mathbf{K}$ into this expression, we have

$$\mathbf{a}^{\mathsf{T}} (\mathbf{K} + \delta\mathbf{I})^{-1} \mathbf{a} = \left(\mathbf{U}^{\mathsf{T}}\mathbf{a}\right)^{\mathsf{T}} (\mathbf{S} + \delta\mathbf{I})^{-1} \left(\mathbf{U}^{\mathsf{T}}\mathbf{a}\right). \tag{3.12}$$

Using Equation 3.8, we can stack the matrix product in blocks involving $\mathbf{U}_1$ and $\mathbf{U}_2$ to re-write this expression as

$$\begin{bmatrix}\mathbf{U}_1^{\mathsf{T}}\mathbf{a} & \mathbf{U}_2^{\mathsf{T}}\mathbf{a}\end{bmatrix}^{\mathsf{T}} \begin{bmatrix} (\mathbf{S}_1 + \delta\mathbf{I}_k)^{-1} & \mathbf{0} \\ \mathbf{0} & (\delta\mathbf{I}_{n-k})^{-1} \end{bmatrix} \begin{bmatrix}\mathbf{U}_1^{\mathsf{T}}\mathbf{a} & \mathbf{U}_2^{\mathsf{T}}\mathbf{a}\end{bmatrix}. \tag{3.13}$$

As the off-diagonal blocks of the central matrix are equal to zero, the quadratic form reduces to the sum of two terms, namely

$$\left(\mathbf{U}_1^{\mathsf{T}}\mathbf{a}\right)^{\mathsf{T}} (\mathbf{S}_1 + \delta\mathbf{I}_k)^{-1} \left(\mathbf{U}_1^{\mathsf{T}}\mathbf{a}\right) + \left(\mathbf{U}_2^{\mathsf{T}}\mathbf{a}\right)^{\mathsf{T}} (\delta\mathbf{I}_{n-k})^{-1} \left(\mathbf{U}_2^{\mathsf{T}}\mathbf{a}\right). \tag{3.14}$$

Substituting $\mathbf{U}_2^{\mathsf{T}}\mathbf{U}_2$ for $\mathbf{I}_{n-k}$ (using Equation 3.11), the second term becomes

$$\left(\mathbf{U}_2^{\mathsf{T}}\mathbf{a}\right)^{\mathsf{T}} (\delta\mathbf{I}_{n-k})^{-1} \left(\mathbf{U}_2^{\mathsf{T}}\mathbf{a}\right) = \frac{1}{\delta}\mathbf{a}^{\mathsf{T}}\mathbf{U}_2\mathbf{I}_{n-k}\mathbf{U}_2^{\mathsf{T}}\mathbf{a} = \frac{1}{\delta}\mathbf{a}^{\mathsf{T}}\mathbf{U}_2 \left(\mathbf{U}_2^{\mathsf{T}}\mathbf{U}_2\right) \mathbf{U}_2^{\mathsf{T}}\mathbf{a}. \tag{3.15}$$

Finally, using Equation 3.10, we can eliminate $\mathbf{U}_2$ to obtain

$$\frac{1}{\delta} \left(\mathbf{U}_2\mathbf{U}_2^{\mathsf{T}}\mathbf{a}\right)^{\mathsf{T}} \left(\mathbf{U}_2\mathbf{U}_2^{\mathsf{T}}\mathbf{a}\right) = \frac{1}{\delta} \left(\left(\mathbf{I}_n - \mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{a}\right)^{\mathsf{T}} \left(\left(\mathbf{I}_n - \mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{a}\right). \tag{3.16}$$

Substituting (3.16) into (3.14), we obtain

$$\mathbf{a}^{\mathsf{T}} (\mathbf{K} + \delta\mathbf{I})^{-1} \mathbf{a} = \left(\mathbf{U}_1^{\mathsf{T}}\mathbf{a}\right)^{\mathsf{T}} (\mathbf{S}_1 + \delta\mathbf{I}_k)^{-1} \left(\mathbf{U}_1^{\mathsf{T}}\mathbf{a}\right) + \frac{1}{\delta} \left(\left(\mathbf{I}_n - \mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{a}\right)^{\mathsf{T}} \left(\left(\mathbf{I}_n - \mathbf{U}_1\mathbf{U}_1^{\mathsf{T}}\right)\mathbf{a}\right). \tag{3.17}$$

Substituting $(\mathbf{y} - \mathbf{X}\boldsymbol{\beta})$ for $\mathbf{a}$, we obtain Equation 3.2.

4 Restricted maximum likelihood

So far the derivations have been limited to maximum likelihood parameter estimation. However, it is straightforward to extend these results to the restricted log likelihood, which comprises the log likelihood (with $\hat{\boldsymbol{\beta}}$ plugged in), plus three additional terms [1]:

$$REMLL_{\mathrm{R}}\left(\sigma_e^2, \sigma_g^2\right) = LL\left(\sigma_e^2, \sigma_g^2, \hat{\boldsymbol{\beta}}\right) + \frac{1}{2}\left(d\log\left(2\pi\sigma_g^2\right) + \log\left|\mathbf{X}^{\mathsf{T}}\mathbf{X}\right| - \log\left|\mathbf{X}^{\mathsf{T}} (\mathbf{K} + \delta\mathbf{I})^{-1} \mathbf{X}\right|\right).$$

Again, using the spectral decomposition of $\mathbf{K}$, the restricted log likelihood becomes

$$REMLL_{\mathrm{R}}\left(\sigma_e^2, \sigma_g^2\right) = LL\left(\sigma_e^2, \sigma_g^2, \hat{\boldsymbol{\beta}}\right) + \frac{1}{2}\left(d\log\left(2\pi\sigma_g^2\right) + \log\left|\mathbf{X}^{\mathsf{T}}\mathbf{X}\right| - \log\left|\left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)^{\mathsf{T}} (\mathbf{S} + \delta\mathbf{I})^{-1} \left(\mathbf{U}^{\mathsf{T}}\mathbf{X}\right)\right|\right).$$

Neglecting the cubic dependence on d for computing the determinants, these additional terms can be evaluated in time complexity $O(n)$. If $\mathbf{K}$ has rank $k < n$, we can evaluate the additional terms in

$O(n+k)$, using the k-spectral decomposition $\mathbf{K} = \mathbf{U}_1\mathbf{S}_1\mathbf{U}_1^{\mathrm{T}}$. For this purpose, we re-use the results from Section 3.3, substituting $\mathbf{X}$ for $\mathbf{a}$, to get

$$REMLL_{\mathrm{R}}\left(\sigma_e^2,\sigma_g^2\right) = LL\left(\sigma_e^2,\sigma_g^2,\hat{\boldsymbol{\beta}}\right) + \frac{1}{2}\left(d\log\left(2\pi\sigma_g^2\right) + \log\left|\mathbf{X}^{\mathrm{T}}\mathbf{X}\right|\right)$$
$$+\frac{1}{2}\left(-\log\left|\left(\mathbf{U}_1^{\mathrm{T}}\mathbf{X}\right)^{\mathrm{T}}\left(\mathbf{S}_1+\delta\mathbf{I}_k\right)^{-1}\left(\mathbf{U}_1^{\mathrm{T}}\mathbf{X}\right) + \frac{1}{\delta}\left(\left(\mathbf{I}_n-\mathbf{U}_1\mathbf{U}_1^{\mathrm{T}}\right)\mathbf{X}\right)^{\mathrm{T}}\left(\left(\mathbf{I}_n-\mathbf{U}_1\mathbf{U}_1^{\mathrm{T}}\right)\mathbf{X}\right)\right|\right).$$

The restricted maximum likelihood (*REML*) variance component estimate is given by

$$\hat{\sigma}_g^2 = \frac{1}{n-d}\sum_{i=1}^{n}\frac{\left([\mathbf{U}^{\mathrm{T}}\mathbf{y}]_i - [\mathbf{U}^{\mathrm{T}}\mathbf{X}]_{i:}\hat{\boldsymbol{\beta}}\right)^2}{[\mathbf{S}]_{ii}+\delta}.$$

The formulas for the remaining parameters remain unchanged. The space requirements for REML are the same as those for ML.

5 FaST-LMM for groups of genetically identical individuals and for compression

FaST-LMM can be made even more efficient when multiple individuals share the same genotype or when the LMM is compressed (as in compressed mixed linear models (CMLM) [7]). In either case, the likelihood can be written as

$$LL\left(\sigma_e^2,\sigma_g^2,\boldsymbol{\beta}\right) = \log\mathcal{N}\left(\mathbf{y}|\mathbf{X}\boldsymbol{\beta};\sigma_g^2\mathbf{Z}\mathbf{K}\mathbf{Z}^{\mathrm{T}}+\sigma_e^2\mathbf{I}\right), \tag{5.1}$$

where $\mathbf{Z}$ is an $n\times g$ binary indicator matrix, that assigns the data for each of n individuals to exactly one of the g groups, and $\mathbf{K}$ is a $g\times g$ between group genetic similarity matrix. The individuals in each group may have the same genotype, or merely a similar genotype as in the case of compression.

In the spirit of FaST-LMM, we look for an efficient way of computing the spectral decomposition of $\mathbf{Z}\mathbf{K}\mathbf{Z}^{\mathrm{T}}$. This spectral decomposition can then be plugged into Formulas 3.4-3.7 as a means to evaluate Equation 5.1, in run time and memory that are linear in the cohort size n. In Section 5.1, we consider the case where genetic similarity is defined by an RRM, given by $\mathbf{Z}\boldsymbol{\Phi}\boldsymbol{\Phi}^{\mathrm{T}}\mathbf{Z}^{\mathrm{T}}$. We show that, given a $g\times s_{\mathrm{c}}$ matrix $\boldsymbol{\Phi}$ of s_{c} SNPs (in the case of compression obtained, e.g., by averaging the SNP data for individuals over the members of each group), the spectral decomposition of the RRM can be computed from the SVD of the $g\times s_{\mathrm{c}}$ matrix $(\mathbf{Z}^{\mathrm{T}}\mathbf{Z})^{1/2}\boldsymbol{\Phi}$ in $O(\min(g,s_{\mathrm{c}})gs_{\mathrm{c}})$ time and $O(gs_{\mathrm{c}})$ memory. (In the case of compression, the same $\boldsymbol{\Phi}\boldsymbol{\Phi}^{\mathrm{T}}$ would be obtained if instead we used a group-wise average of the $n\times n$ RRM.) In Section 5.2, we consider arbitrary genetic similarity. We prove that, given any $g\times g$ positive semi-definite group similarity matrix $\mathbf{K}$, the spectral decomposition of the $n\times n$ matrix $\mathbf{Z}\mathbf{K}\mathbf{Z}^{\mathrm{T}}$ can be computed from the spectral decomposition of the much smaller $g\times g$ matrix $(\mathbf{Z}^{\mathrm{T}}\mathbf{Z})^{1/2}\mathbf{K}(\mathbf{Z}^{\mathrm{T}}\mathbf{Z})^{1/2}$ using $O(g^3)$ time and $O(g^2)$ memory.

5.1 Spectral decomposition of $\mathbf{Z\Phi\Phi^T Z^T}$

Let $\mathbf{\Phi}$ be the $g \times s_c$ matrix of SNP data. Let $\mathbf{Z}$ be the $n \times g$ group indicator matrix that assigns data for each of n individuals to exactly one group. Then the genetic similarity matrix becomes $\mathbf{Z\Phi\Phi^T Z^T}$.

For our argument, we use the fact that, given a matrix $\mathbf{A}$, both $\mathbf{AA^T}$ as well as $\mathbf{A^TA}$ share the same eigenvalues, and that these eigenvalues are given by the square of the singular values of $\mathbf{A}$. The eigenvectors of $\mathbf{AA^T}$ are given by the left singular vectors of $\mathbf{A}$; and the eigenvectors of $\mathbf{A^TA}$ are given by the right singular vectors of $\mathbf{A}$. So the eigenvalues of $\mathbf{Z\Phi\Phi^T Z^T}$ are the same as the eigenvalues of $\mathbf{\Phi^T Z^T Z\Phi} = \mathbf{\Phi^T}(\mathbf{Z^TZ})^{1/2}(\mathbf{Z^TZ})^{1/2}\mathbf{\Phi}$. Using the same argument, the latter matrix has the same eigenvalues as $(\mathbf{Z^TZ})^{1/2}\mathbf{\Phi\Phi^T}(\mathbf{Z^TZ})^{1/2}$. These eigenvalues are given by the square of the singular values of $(\mathbf{Z^TZ})^{1/2}\mathbf{\Phi}$, where $(\mathbf{Z^TZ})^{1/2}$ is a $g \times g$ diagonal matrix holding the square root of the number of members of each group on the diagonal. Because $(\mathbf{Z^TZ})^{1/2}$ is diagonal, multiplication can be done in $O(gs_c)$ time.

Let $\tilde{\mathbf{U}}\tilde{\mathbf{S}}\mathbf{V^T}$ be the SVD of $(\mathbf{Z^TZ})^{1/2}\mathbf{\Phi}$. Then the following holds:

$$\mathbf{Z\Phi\Phi^T Z^T} = \mathbf{Z}(\mathbf{Z^TZ})^{-1/2}(\mathbf{Z^TZ})^{1/2}\mathbf{\Phi\Phi^T}(\mathbf{Z^TZ})^{1/2}(\mathbf{Z^TZ})^{-1/2}\mathbf{Z^T}, \tag{5.2}$$

where $(\mathbf{Z^TZ})^{-1/2}$ is a $g \times g$ diagonal matrix, holding one over the square root of the number of members of each group on its diagonal. Substituting $(\mathbf{Z^TZ})^{1/2}\mathbf{\Phi}$ by its SVD, we get

$$\mathbf{Z}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}}\tilde{\mathbf{S}}\mathbf{V^T}\mathbf{V}\tilde{\mathbf{S}}\tilde{\mathbf{U}}^{\mathbf{T}}(\mathbf{Z^TZ})^{-1/2}\mathbf{Z^T}.$$

Finally, by orthonormality of $\mathbf{V}$, this expression simplifies to

$$\mathbf{Z}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}}\mathbf{S}\tilde{\mathbf{U}}^{\mathbf{T}}(\mathbf{Z^TZ})^{-1/2}\mathbf{Z^T}, \tag{5.3}$$

where $\mathbf{S} = \tilde{\mathbf{S}}^2$ is a diagonal matrix, holding the non-zero eigenvalues of $\mathbf{\Phi\Phi^T}$ on its diagonal. The columns of $\mathbf{Z}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}}$ are orthonormal, as can be seen by

$$\tilde{\mathbf{U}}^{\mathbf{T}}(\mathbf{Z^TZ})^{-1/2}\mathbf{Z^TZ}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}} = \tilde{\mathbf{U}}^{\mathbf{T}}(\mathbf{Z^TZ})(\mathbf{Z^TZ})^{-1}\tilde{\mathbf{U}} = \tilde{\mathbf{U}}^{\mathbf{T}}\tilde{\mathbf{U}} = \mathbf{I}_g. \tag{5.4}$$

where we have once again used the fact that $(\mathbf{Z^TZ})$ is diagonal. It follows that $\mathbf{Z}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}}$ holds the eigenvectors of $\mathbf{Z\Phi\Phi^T Z^T}$, completing the spectral decomposition of $\mathbf{Z\Phi\Phi^T Z}$. Note that the rotation of the data by $(\mathbf{Z}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}})^{\mathbf{T}}$ can be done efficiently by multiplying the data by the transpose of the rows of $(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}}$ belonging to the respective group.

5.2 Spectral decomposition of $\mathbf{ZKZ^T}$, when the factors are not known

Here we extend the arguments in Section 5.1 to any positive semi-definite $g \times g$ group genetic similarity matrix $\mathbf{K}$. In this case, the spectral decomposition of $\mathbf{ZKZ^T} = \mathbf{USU^T}$ can also be computed efficiently, namely from the spectral decomposition of $(\mathbf{Z^TZ})^{1/2}\mathbf{K}(\mathbf{Z^TZ})^{1/2} = \tilde{\mathbf{U}}\mathbf{S}\tilde{\mathbf{U}}^{\mathbf{T}}$, which can be computed in $O(g^3)$ run time. As $\mathbf{K}$ is positive semi-definite, there always exists some square root $\mathbf{\Phi}$ of $\mathbf{K}$, such that $\mathbf{K} = \mathbf{\Phi\Phi^T}$. In Section 5.1, we have shown, that $\mathbf{ZKZ^T}$ and $(\mathbf{Z^TZ})^{1/2}\mathbf{K}(\mathbf{Z^TZ})^{1/2}$ have the same eigenvalues. Consequently, we can compute the eigenvalues $\mathbf{S}$ of $\mathbf{ZKZ^T}$ from the spectral decomposition $\tilde{\mathbf{U}}\mathbf{S}\tilde{\mathbf{U}}^{\mathbf{T}}$. Analogous to the derivation in Equations 5.2-5.3, it follows that the eigenvectors of $\mathbf{ZKZ^T}$ are $\mathbf{Z}(\mathbf{Z^TZ})^{-1/2}\tilde{\mathbf{U}}$, where by Equation 5.4, the columns are orthonormal.

References

[1] Kang, H. M. *et al.* Efficient control of population structure in model organism association mapping. *Genetics* **107** (2008).

[2] Kang, H. M. *et al.* Variance component model to account for sample structure in genome-wide association studies. *Nat. Genet.* **42**, 348–354 (2010).

[3] Price, A. L. *et al.* Principal components analysis corrects for stratification in genome-wide association studies. *Nature genetics* **38**, 904–909 (2006).

[4] Tipping, M. & Bishop, C. M. Probabilistic principal component analysis. *J.R. Statistical Society, Series B* **61**, 6111–622 (1999).

[5] Wall, M. E., Rechtsteiner, A. & Rocha, L. M. *A Practical Approach to Microarray Data Analysis* (Kluwer, Norwell, MA, 2003).

[6] Yang, J. *et al.* Common SNPs explain a large proportion of the heritability for human height. *Nat. Genet.* **42**, 565–569 (2010).

[7] Zhang, Z. *et al.* Mixed linear model approach adapted for genome-wide association studies. *Nat. Genet.* **42**, 355–360 (2010).

Supplementary Note 2: Null-Model Contamination

In our experiments measuring the accuracy of association P values in the main paper, the SNPs being tested and the SNPs used to estimate genetic similarity were deliberately made disjoint. Here, we discuss the reason for this approach.

As discussed in the main paper, a LMM with no fixed effects using an RRM constructed from a set of SNPs is equivalent to a linear regression of the SNPs on the phenotype, with linear weights (i.e., SNP effects) integrated over independent Normal distributions having the same variance [1]. So, by using a LMM with an RRM to test a given SNP for an association with the phenotype, we are in effect adjusting for *background SNPs,* precisely those used to construct the RMM. Thus, when testing a given SNP, using that SNP in the computation of the RRM would be equivalent to using that SNP as a regressor in the null model, making the log likelihood of the null-model higher than it should be, thus making the P value higher than it should be. We call this phenomenon *null-model contamination.* A weaker form of this phenomenon could exist due to linkage disequilibrium.

In this note, we show that, on the WTCCC data for the CD phenotype with non-white individuals and close family members included, this effect produces substantially deflated P values as measured by the λ statistic, and quantify the degree to which LD plays a role. In an ideal experiment, we would compare the λ statistic for two association tests of each available SNP, one where the RRM is constructed from all SNPs, and one where the RRM is constructed from all SNPs but the SNP being tested (and those nearby having at least a certain amount of LD with it). Unfortunately, such a comparison is computationally infeasible, as it would require the construction of many thousands of RRMs and their corresponding spectral decompositions.

Instead, we used an approach where the SNPs used to construct the RRM were chosen to be systematically further and further away from a set of test SNPs, while holding the number of SNPs used to construct the RRM (i.e., the number of background SNPs in the equivalent linear regression) constant. In particular, after ordering SNPs by their position, we used every thirty-second SNP starting from the i^{th} SNP in each chromosome to form a set of test SNPs. In addition, we created six sets of SNPs to construct RRMs, each set lying further away from the set of test SNPs. In a given set, we included every thirty-second SNP starting at the $i + j^{\text{th}}$ SNP in each chromosome, $j = 0, 1, 2, 4, 8$, and 16. This experiment was performed for $i = 1, 2, 3, 4$, and 5. Each set of SNPs contained approximately 11K SNPs. As shown in **Fig. 1**, λ generally increased with j for $j \leq 8$, beyond which LD presumably had little effect. Note that the values for λ for the experiments having the greatest amount of null contamination ($j = 0$) were quite similar to those when all 367K SNPs were used to construct the RRM (differences were less than 0.027 over all values of i), suggesting that our experiment did not deviate substantially from the idealized one.

These experiments show that null-model contamination can be a substantial effect. Consequently, when using a LMM to test whether a given SNP is associated with the phenotype, the RRM should be computed from all SNPs except for those in close proximity to the test SNP. As this approach is again computationally infeasible, in our experiments in the main paper evaluating the accuracy of association P values, we tested SNPs on chromosome 1 and constructed the "gold-standard" RRM from all SNPs on all but chromosome 1. We used chromosome 1 because it has a large number of

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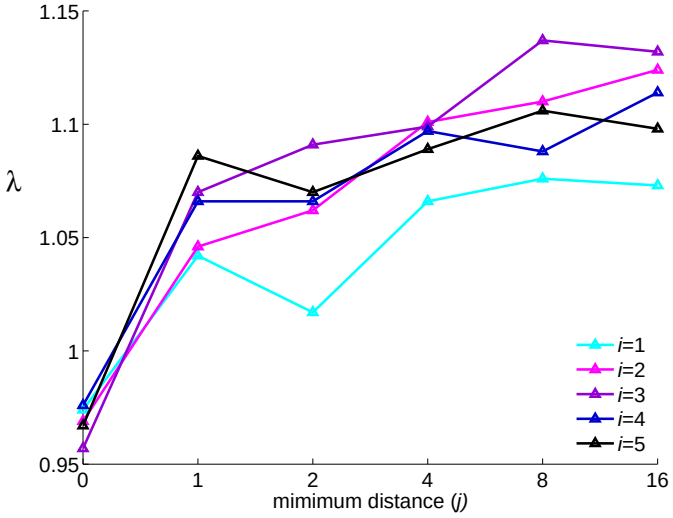

Figure 1: The λ statistic as a function of the minimum distance between a SNP in the test set and a SNP in the set used to construct the RRM. Each set of SNPs was selected by incorporating every thirty-second SNP along each chromosome starting at position i.

SNPs for testing and because there were enough genome-wide significant SNPs to assess the effects of sampling on calls of significance.

References

[1] Goddard, M. E., Wray, N., Verbyla, K. & Visscher, P. M. Estimating effects and making predictions from genome-wide marker data. *Statis. Sci* **24**, 517–529 (2009).

Nature Methods:doi10.1038/nmeth.1681