

S1 Text

Block Coordinate Descent Algorithm

Model Set-up

Let $i = 1, \dots, N$ be a grouping index, $j = 1, \dots, n_i$ the observation index within a group and $N_T = \sum_{i=1}^N n_i$ the total number of observations. For each group let $\mathbf{y}_i = (y_1, \dots, y_{n_i})$ be the observed vector of responses or phenotypes, \mathbf{X}_i an $n_i \times (p+1)$ design matrix (with the column of 1s for the intercept), \mathbf{b}_i a group-specific random effect vector of length n_i and $\boldsymbol{\varepsilon}_i = (\varepsilon_{i1}, \dots, \varepsilon_{in_i})$ the individual error terms. Denote the stacked vectors $\mathbf{Y} = (\mathbf{y}_1, \dots, \mathbf{y}_N)^T \in \mathbb{R}^{N_T \times 1}$, $\mathbf{b} = (\mathbf{b}_1, \dots, \mathbf{b}_N)^T \in \mathbb{R}^{N_T \times 1}$, $\boldsymbol{\varepsilon} = (\boldsymbol{\varepsilon}_1, \dots, \boldsymbol{\varepsilon}_N)^T \in \mathbb{R}^{N_T \times 1}$, and the stacked matrix $\mathbf{X} = (\mathbf{X}_1^T, \dots, \mathbf{X}_N^T) \in \mathbb{R}^{N_T \times (p+1)}$. Furthermore, let $\boldsymbol{\beta} = (\beta_0, \beta_1, \dots, \beta_p)^T \in \mathbb{R}^{(p+1) \times 1}$ be a vector of fixed effects regression coefficients corresponding to \mathbf{X} . We consider the following linear mixed model with a single random effect [1]:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{b} + \boldsymbol{\varepsilon} \quad (1)$$

where the random effect \mathbf{b} and the error variance $\boldsymbol{\varepsilon}$ are assigned the distributions

$$\mathbf{b} \sim \mathcal{N}(0, \eta\sigma^2\boldsymbol{\Phi}) \quad \boldsymbol{\varepsilon} \sim \mathcal{N}(0, (1-\eta)\sigma^2\mathbf{I}) \quad (2)$$

Here, $\boldsymbol{\Phi}_{N_T \times N_T}$ is a known positive semi-definite and symmetric covariance or kinship matrix calculated from SNPs sampled across the genome, $\mathbf{I}_{N_T \times N_T}$ is the identity matrix and parameters σ^2 and $\eta \in [0, 1]$ determine how the variance is divided between \mathbf{b} and $\boldsymbol{\varepsilon}$. Note that η is also the narrow-sense heritability (h^2), defined as the proportion of phenotypic variance attributable to the additive genetic factors [2]. The joint density of \mathbf{Y} is therefore

multivariate normal:

$$\mathbf{Y} | (\boldsymbol{\beta}, \eta, \sigma^2) \sim \mathcal{N}(\mathbf{X}\boldsymbol{\beta}, \eta\sigma^2\boldsymbol{\Phi} + (1 - \eta)\sigma^2\mathbf{I}) \quad (3)$$

We consider the parameterization in (3) since maximization is easier over the compact set $\eta \in [0, 1]$ than over the unbounded interval $\delta \in [0, \infty)$ [1]. We define the complete parameter vector as $\boldsymbol{\Theta} := (\boldsymbol{\beta}, \eta, \sigma^2)$. The negative log-likelihood for (3) is given by

$$-\ell(\boldsymbol{\Theta}) \propto \frac{N_T}{2} \log(\sigma^2) + \frac{1}{2} \log(\det(\mathbf{V})) + \frac{1}{2\sigma^2} (\mathbf{Y} - \mathbf{X}\boldsymbol{\beta})^T \mathbf{V}^{-1} (\mathbf{Y} - \mathbf{X}\boldsymbol{\beta}) \quad (4)$$

where $\mathbf{V} = \eta\boldsymbol{\Phi} + (1 - \eta)\mathbf{I}$ and $\det(\mathbf{V})$ is the determinant of \mathbf{V} . Let $\boldsymbol{\Phi} = \mathbf{U}\mathbf{D}\mathbf{U}^T$ be the eigen (spectral) decomposition of the kinship matrix $\boldsymbol{\Phi}$, where $\mathbf{U}_{N_T \times N_T}$ is an orthonormal matrix of eigenvectors (i.e. $\mathbf{U}\mathbf{U}^T = \mathbf{I}$) and $\mathbf{D}_{N_T \times N_T}$ is a diagonal matrix of eigenvalues Λ_i . In the main text we show that \mathbf{V} can then be further simplified to

$$\mathbf{V} = \mathbf{U}\tilde{\mathbf{D}}\mathbf{U}^T \quad (5)$$

where

$$\tilde{\mathbf{D}} = \text{diag} \{1 + \eta(\Lambda_1 - 1), 1 + \eta(\Lambda_2 - 1), \dots, 1 + \eta(\Lambda_{N_T} - 1)\} \quad (6)$$

Since (6) is a diagonal matrix, its inverse is also a diagonal matrix:

$$\tilde{\mathbf{D}}^{-1} = \text{diag} \left\{ \frac{1}{1 + \eta(\Lambda_1 - 1)}, \frac{1}{1 + \eta(\Lambda_2 - 1)}, \dots, \frac{1}{1 + \eta(\Lambda_{N_T} - 1)} \right\} \quad (7)$$

From (5) and (6), $\log(\det(\mathbf{V}))$ simplifies to

$$\begin{aligned}\log(\det(\mathbf{V})) &= \log\left(\det(\mathbf{U}) \det(\tilde{\mathbf{D}}) \det(\mathbf{U}^T)\right) \\ &= \log\left\{\prod_{i=1}^{N_T} (1 + \eta(\Lambda_i - 1))\right\} \\ &= \sum_{i=1}^{N_T} \log(1 + \eta(\Lambda_i - 1))\end{aligned}\tag{8}$$

since $\det(\mathbf{U}) = 1$. It also follows from (5) that

$$\begin{aligned}\mathbf{V}^{-1} &= (\mathbf{U}\tilde{\mathbf{D}}\mathbf{U}^T)^{-1} \\ &= (\mathbf{U}^T)^{-1} (\tilde{\mathbf{D}})^{-1} \mathbf{U}^{-1} \\ &= \mathbf{U}\tilde{\mathbf{D}}^{-1}\mathbf{U}^T\end{aligned}\tag{9}$$

since for an orthonormal matrix $\mathbf{U}^{-1} = \mathbf{U}^T$. Substituting (7), (8) and (9) into (4) the negative log-likelihood becomes

$$-\ell(\boldsymbol{\Theta}) = \frac{N_T}{2} \log(\sigma^2) + \frac{1}{2} \sum_{i=1}^{N_T} \log(1 + \eta(\Lambda_i - 1)) + \frac{1}{2\sigma^2} \sum_{i=1}^{N_T} \frac{\left(\tilde{Y}_i - \sum_{j=0}^p \tilde{X}_{ij+1}\beta_j\right)^2}{1 + \eta(\Lambda_i - 1)}\tag{10}$$

where $\tilde{\mathbf{Y}} = \mathbf{U}^T \mathbf{Y}$, $\tilde{\mathbf{X}} = \mathbf{U}^T \mathbf{X}$, \tilde{Y}_i denotes the i^{th} element of $\tilde{\mathbf{Y}}$, \tilde{X}_{ij} is the i, j^{th} entry of $\tilde{\mathbf{X}}$ and $\mathbf{1}$ is a column vector of N_T ones.

Penalized Maximum Likelihood Estimator

We define the $p + 3$ length vector of parameters $\boldsymbol{\Theta} := (\Theta_0, \Theta_1, \dots, \Theta_{p+1}, \Theta_{p+2}, \Theta_{p+3}) = (\boldsymbol{\beta}, \eta, \sigma^2)$ where $\boldsymbol{\beta} \in \mathbb{R}^{p+1}$, $\eta \in [0, 1]$, $\sigma^2 > 0$. In what follows, $p + 2$ and $p + 3$ are the indices in $\boldsymbol{\Theta}$ for η and σ^2 , respectively. In light of our goals to select variables associated with the response in high-dimensional data, we propose to place a constraint on the magnitude of the regression coefficients. This can be achieved by adding a penalty term to the likelihood

function (10). The penalty term is a necessary constraint because in our applications, the sample size is much smaller than the number of predictors. We define the following objective function:

$$Q_\lambda(\Theta) = f(\Theta) + \lambda \sum_{j \neq 0} v_j P_j(\beta_j) \quad (11)$$

where $f(\Theta) := -\ell(\Theta)$ is defined in (10), $P_j(\cdot)$ is a penalty term on the fixed regression coefficients $\beta_1, \dots, \beta_{p+1}$ (we do not penalize the intercept) controlled by the nonnegative regularization parameter λ , and v_j is the penalty factor for j th covariate. These penalty factors serve as a way of allowing parameters to be penalized differently. Note that we do not penalize η or σ^2 . An estimate of the regression parameters $\hat{\Theta}_\lambda$ is obtained by

$$\hat{\Theta}_\lambda = \arg \min_{\Theta} Q_\lambda(\Theta) \quad (12)$$

We use a general purpose block coordinate descent algorithm (CGD) [3] to solve (12). At each iteration, the algorithm approximates the negative log-likelihood $f(\cdot)$ in $Q_\lambda(\cdot)$ by a strictly convex quadratic function and then applies block coordinate descent to generate a decent direction followed by an inexact line search along this direction [3]. For continuously differentiable $f(\cdot)$ and convex and block-separable $P(\cdot)$ (i.e. $P(\beta) = \sum_i P_i(\beta_i)$), [3] show that the solution generated by the CGD method is a stationary point of $Q_\lambda(\cdot)$ if the coordinates are updated in a Gauss-Seidel manner i.e. $Q_\lambda(\cdot)$ is minimized with respect to one parameter while holding all others fixed. The CGD algorithm can thus be run in parallel and therefore suited for large p settings. It has been successfully applied in fixed effects models (e.g. [4], [5]) and [6] for mixed models with an ℓ_1 penalty. Following Tseng and Yun [3], the CGD algorithm is given by Algorithm 1.

Algorithm 1: Coordinate Gradient Descent Algorithm to solve (12)

Set the iteration counter $k \leftarrow 0$ and choose initial values for the parameter vector

$\Theta^{(0)}$;

repeat

Approximate the Hessian $\nabla^2 f(\Theta^{(k)})$ by a symmetric matrix $H^{(k)}$:

$$H^{(k)} = \text{diag} \left[\min \left\{ \max \left\{ \left[\nabla^2 f(\Theta^{(k)}) \right]_{jj}, c_{\min} \right\}, c_{\max} \right\} \right]_{j=1, \dots, p} \quad (13)$$

for $j = 1, \dots, p$ **do**

Solve the descent direction $d^{(k)} := d_{H^{(k)}}(\Theta_j^{(k)})$;

if $\Theta_j^{(k)} \in \{\beta_1, \dots, \beta_p\}$ **then**

$$d_{H^{(k)}}(\Theta_j^{(k)}) \leftarrow \arg \min_d \left\{ \nabla f(\Theta_j^{(k)})d + \frac{1}{2}d^2 H_{jj}^{(k)} + \lambda P(\Theta_j^{(k)} + d) \right\} \quad (14)$$

end

end

Choose a stepsize;

$$\alpha_j^{(k)} \leftarrow \text{line search given by the Armijo rule}$$

Update;

$$\hat{\Theta}_j^{(k+1)} \leftarrow \hat{\Theta}_j^{(k)} + \alpha_j^{(k)} d^{(k)}$$

Update;

$$\hat{\eta}^{(k+1)} \leftarrow \arg \min_{\eta} \frac{1}{2} \sum_{i=1}^{N_T} \log(1 + \eta(\Lambda_i - 1)) + \frac{1}{2\sigma^2^{(k)}} \sum_{i=1}^{N_T} \frac{\left(\tilde{Y}_i - \sum_{j=0}^p \tilde{X}_{ij+1} \beta_j^{(k+1)} \right)^2}{1 + \eta(\Lambda_i - 1)} \quad (15)$$

Update;

$$\hat{\sigma}^2^{(k+1)} \leftarrow \frac{1}{N_T} \sum_{i=1}^{N_T} \frac{\left(\tilde{Y}_i - \sum_{j=0}^p \tilde{X}_{ij+1} \beta_j^{(k+1)} \right)^2}{1 + \eta^{(k+1)}(\Lambda_i - 1)} \quad (16)$$

$k \leftarrow k + 1$

until convergence criterion is satisfied;

The Armijo rule is defined as follows [3]:

Choose $\alpha_{init}^{(k)} > 0$ and let $\alpha^{(k)}$ be the largest element of $\{\alpha_{init}^k \delta^r\}_{r=0,1,2,\dots}$ satisfying

$$Q_\lambda(\Theta_j^{(k)} + \alpha^{(k)} d^{(k)}) \leq Q_\lambda(\Theta_j^{(k)}) + \alpha^{(k)} \varrho \Delta^{(k)} \quad (17)$$

where $0 < \delta < 1$, $0 < \varrho < 1$, $0 \leq \gamma < 1$ and

$$\Delta^{(k)} := \nabla f(\Theta_j^{(k)}) d^{(k)} + \gamma (d^{(k)})^2 H_{jj}^{(k)} + \lambda P(\Theta_j^{(k)} + d^{(k)}) - \lambda P(\Theta_j^{(k)}) \quad (18)$$

Common choices for the constants are $\delta = 0.1$, $\varrho = 0.001$, $\gamma = 0$, $\alpha_{init}^{(k)} = 1$ for all k [6].

Below we detail the specifics of Algorithm 1 for the ℓ_1 penalty.

ℓ_1 penalty

The objective function is given by

$$Q_\lambda(\Theta) = f(\Theta) + \lambda |\beta| \quad (19)$$

Descent Direction

For simplicity, we remove the iteration counter (k) from the derivation below.

For $\Theta_j^{(k)} \in \{\beta_1, \dots, \beta_p\}$, let

$$d_H(\Theta_j) = \arg \min_d G(d) \quad (20)$$

where

$$G(d) = \nabla f(\Theta_j) d + \frac{1}{2} d^2 H_{jj} + \lambda |\Theta_j + d|$$

Since $G(d)$ is not differentiable at $-\Theta_j$, we calculate the subdifferential $\partial G(d)$ and search for d with $0 \in \partial G(d)$:

$$\partial G(d) = \nabla f(\Theta_j) + d H_{jj} + \lambda u \quad (21)$$

where

$$u = \begin{cases} 1 & \text{if } d > -\Theta_j \\ -1 & \text{if } d < -\Theta_j \\ [-1, 1] & \text{if } d = \Theta_j \end{cases} \quad (22)$$

We consider each of the three cases in (21) below

1. $d > -\Theta_j$

$$\begin{aligned} \partial G(d) &= \nabla f(\Theta_j) + dH_{jj} + \lambda = 0 \\ d &= \frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} \end{aligned}$$

Since $\lambda > 0$ and $H_{jj} > 0$, we have

$$\frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}} > \frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} = d \stackrel{\text{def}}{>} -\Theta_j$$

The solution can be written compactly as

$$d = \text{mid} \left\{ \frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}}, -\Theta_j, \frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} \right\}$$

where $\text{mid} \{a, b, c\}$ denotes the median (mid-point) of a, b, c [3].

2. $d < -\Theta_j$

$$\begin{aligned} \partial G(d) &= \nabla f(\Theta_j) + dH_{jj} - \lambda = 0 \\ d &= \frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}} \end{aligned}$$

Since $\lambda > 0$ and $H_{jj} > 0$, we have

$$\frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} < \frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}} = d \stackrel{\text{def}}{<} -\Theta_j$$

Again, the solution can be written compactly as

$$d = \text{mid} \left\{ \frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}}, -\Theta_j, \frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} \right\}$$

3. $d_j = -\Theta_j$

There exists $u \in [-1, 1]$ such that

$$\begin{aligned} \partial G(d) &= \nabla f(\Theta_j) + dH_{jj} + \lambda u = 0 \\ d &= \frac{-(\nabla f(\Theta_j) + \lambda u)}{H_{jj}} \end{aligned}$$

For $-1 \leq u \leq 1$, $\lambda > 0$ and $H_{jj} > 0$ we have

$$\frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} \leq d \stackrel{\text{def}}{=} -\Theta_j \leq \frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}}$$

The solution can again be written compactly as

$$d = \text{mid} \left\{ \frac{-(\nabla f(\Theta_j) - \lambda)}{H_{jj}}, -\Theta_j, \frac{-(\nabla f(\Theta_j) + \lambda)}{H_{jj}} \right\}$$

We see all three cases lead to the same solution for (20). Therefore the descent direction for $\Theta_j^{(k)} \in \{\beta_1, \dots, \beta_p\}$ for the ℓ_1 penalty is given by

$$d = \text{mid} \left\{ \frac{-(\nabla f(\beta_j) - \lambda)}{H_{jj}}, -\beta_j, \frac{-(\nabla f(\beta_j) + \lambda)}{H_{jj}} \right\} \quad (23)$$

Solution for the β parameter

If the Hessian $\nabla^2 f(\Theta^{(k)}) > 0$ then $H^{(k)}$ defined in (13) is equal to $\nabla^2 f(\Theta^{(k)})$. Using $\alpha_{init} = 1$, the largest element of $\left\{ \alpha_{init}^{(k)} \delta^r \right\}_{r=0,1,2,\dots}$ satisfying the Armijo Rule inequality is reached for

$\alpha^{(k)} = \alpha_{init}^{(k)} \delta^0 = 1$. The Armijo rule update for the β parameter is then given by

$$\beta_j^{(k+1)} \leftarrow \beta_j^{(k)} + d^{(k)}, \quad j = 1, \dots, p \quad (24)$$

Substituting the descent direction given by (23) into (24) we get

$$\beta_j^{(k+1)} = \text{mid} \left\{ \beta_j^{(k)} + \frac{-(\nabla f(\beta_j^{(k)}) - \lambda)}{H_{jj}}, 0, \beta_j^{(k)} + \frac{-(\nabla f(\beta_j^{(k)}) + \lambda)}{H_{jj}} \right\} \quad (25)$$

We can further simplify this expression. Let

$$w_i := \frac{1}{\sigma^2 (1 + \eta(\Lambda_i - 1))} \quad (26)$$

.

Re-write the part depending on β of the negative log-likelihood in (10) as

$$g(\beta^{(k)}) = \frac{1}{2} \sum_{i=1}^{N_T} w_i \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} - \tilde{X}_{ij} \beta_j^{(k)} \right)^2 \quad (27)$$

The gradient and Hessian are given by

$$\nabla f(\beta_j^{(k)}) := \frac{\partial}{\partial \beta_j^{(k)}} g(\beta^{(k)}) = - \sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} - \tilde{X}_{ij} \beta_j^{(k)} \right) \quad (28)$$

$$H_{jj} := \frac{\partial^2}{\partial \beta_j^{(k)2}} g(\beta^{(k)}) = \sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2 \quad (29)$$

Substituting (28) and (29) into $\beta_j^{(k)} + \frac{-(\nabla f(\beta_j^{(k)}) - \lambda)}{H_{jj}}$

$$\begin{aligned}
& \beta_j^{(k)} + \frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} - \tilde{X}_{ij} \beta_j^{(k)} \right) + \lambda}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} \\
&= \beta_j^{(k)} + \frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} \right) + \lambda}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} - \frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2 \beta_j^{(k)}}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} \\
&= \frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} \right) + \lambda}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} \tag{30}
\end{aligned}$$

Similarly, substituting (28) and (29) in $\beta_j^{(k)} + \frac{-(\nabla f(\beta_j^{(k)}) + \lambda)}{H_{jj}}$ we get

$$\frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} \right) - \lambda}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} \tag{31}$$

Finally, substituting (30) and (31) into (25) we get

$$\begin{aligned}
\beta_j^{(k+1)} &= \text{mid} \left\{ \frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} \right) - \lambda}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2}, 0, \frac{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} \right) + \lambda}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} \right\} \\
&= \frac{\mathcal{S}_\lambda \left(\sum_{i=1}^{N_T} w_i \tilde{X}_{ij} \left(\tilde{Y}_i - \sum_{\ell \neq j} \tilde{X}_{i\ell} \beta_\ell^{(k)} \right) \right)}{\sum_{i=1}^{N_T} w_i \tilde{X}_{ij}^2} \tag{32}
\end{aligned}$$

Where $\mathcal{S}_\lambda(x)$ is the soft-thresholding operator

$$\mathcal{S}_\lambda(x) = \text{sign}(x)(|x| - \lambda)_+$$

$\text{sign}(x)$ is the signum function

$$\text{sign}(x) = \begin{cases} -1 & x < 0 \\ 0 & x = 0 \\ 1 & x > 0 \end{cases}$$

and $(x)_+ = \max(x, 0)$.

References

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