Bayesian multiple logistic regression improves loci prioritization and finemapping in case-control GWAS

Saikat Banerjee[1], Lingyao Zeng[2], Heribert Schunkert[2] and Johannes Söding[*,1]

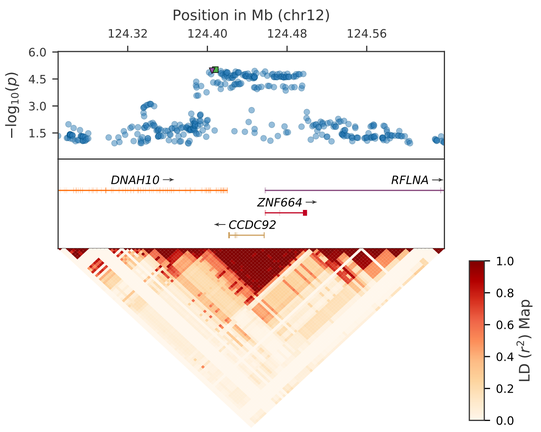
[1]Max Planck Institute for Biophysical Chemistry, 37077 Göttingen, Germany

[2]German Heart Centre, 80636 Munich, Germany

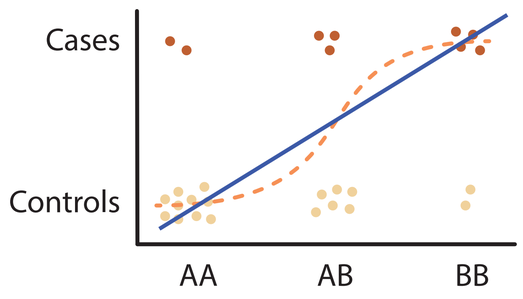
saikat.banerjee@mpibpc.mpg.de, soeding@mpibpc.mpg.de

https://github.com/soedinglab/b-lore

1. Post-GWAS analyses using multiple regression could not utilize the benefits of logistic model



Linkage disequilibrium ☹



Linear model ☹

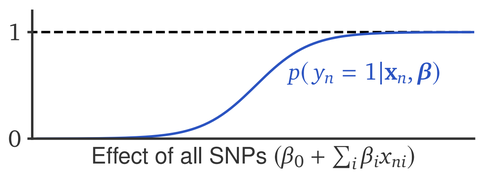
Challenges for using multiple logistic regression:

- The integration for the maximum likelihood cannot be solved analytically.
- MCMC sampling is computationally intractable.
- Solutions using Laplace and linear approximations essentially makes it a linear model.
- Metaanalysis requires knowledge of LD structure of the population.
- Limited to application on each individual genome-wide significant locus

2. B-LORE uses logistic model and sparsity-inducing priors

Probability of n^{th} individual with genotype $\mathbf{x}_n$ to be diseased:

$$p\left(y_n = 1 \mid \mathbf{x}_n, \boldsymbol{\beta}\right) = \frac{\exp\left(\boldsymbol{\beta}^{\mathsf{T}}\mathbf{x}_n\right)}{1 + \exp\left(\boldsymbol{\beta}^{\mathsf{T}}\mathbf{x}_n\right)}$$



Prior on effect sizes given hyperparameters π and σ,
$p\left(\beta_i \mid \pi, \sigma\right)$

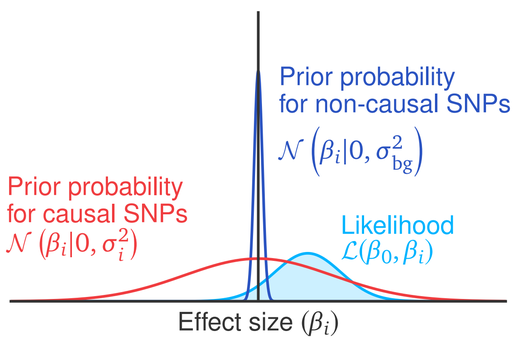
$$= \overbrace{\pi\,\mathcal{N}\left(\beta_i \mid 0, \sigma^2\right)}^{\text{Causal}} + \overbrace{(1-\pi)\,\delta_0}^{\text{Non-causal}}$$

$$= \sum_{z_i=0,1} \pi^{z_i}(1-\pi)^{(1-z_i)}\mathcal{N}\left(\beta_i \mid \mathbf{0}, \operatorname{diag}(\boldsymbol{\sigma}^2_{\mathbf{z},\mathbf{i}})\right)$$

$$= \sum_{z_i=0,1} p\left(\mathbf{z} \mid \pi\right)\mathcal{N}\left(\beta_i \mid \mathbf{0}, \operatorname{diag}(\boldsymbol{\sigma}^2_{\mathbf{z},\mathbf{i}})\right)$$

where, $\sigma^2_{\mathbf{z},i} = z_i\sigma^2$

$z_i \in \{0, 1\} \Rightarrow$ Indicator variable of causality



- $z_i = 1$ SNP i is causal
- $z_i = 0$ SNP i is non-causal

3. We introduce the quasi-Laplace approximation

Evidence approximation: maximizing the marginal likelihood

$$\mathrm{m}\mathcal{L}(\pi, \sigma) := p\left(\mathbf{y} \mid \mathbf{x}, \pi, \sigma\right) = \sum_{\mathbf{z}} p\left(\mathbf{z} \mid \pi\right) \int p\left(\mathbf{y} \mid \mathbf{x}, \boldsymbol{\beta}\right)\mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \operatorname{diag}\left(\boldsymbol{\sigma}^2_{\mathbf{z}}\right)\right)d\boldsymbol{\beta} \rightarrow \max$$

Quasi-Laplace approximation:

$$p\left(\mathbf{y} \mid \mathbf{x}, \boldsymbol{\beta}\right)\mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \operatorname{diag}\left(\boldsymbol{\sigma}^2_{\mathbf{z}}\right)\right) = \underbrace{p\left(\mathbf{y} \mid \mathbf{x}, \boldsymbol{\beta}\right)\mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \tilde{\sigma}^2\mathbb{I}\right)}_{\propto\, \mathcal{N}\left(\boldsymbol{\beta} \mid \tilde{\boldsymbol{\beta}}, \tilde{\boldsymbol{\Lambda}}^{-1}\right)} \frac{\mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \operatorname{diag}\left(\boldsymbol{\sigma}^2_{\mathbf{z}}\right)\right)}{\mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0}, \tilde{\sigma}^2\mathbb{I}\right)}$$

Benefits:

- The regularizer pulls the maximum of the regularized likelihood near to the mode of the integral, making it more accurate than Laplace approximation.
- Can be extended to multiple studies.
- Fast gradient-descent optimization.

B-LORE schema

1. Two-step optimization at each cohort to estimate $\tilde{\sigma}$ and $(\tilde{\boldsymbol{\beta}}, \tilde{\boldsymbol{\Lambda}})$.
2. Estimation of hyperparameters (π, σ).

4. Inference

Prediction of causality of each locus.

The probability for a locus to be causally associated with the disease is

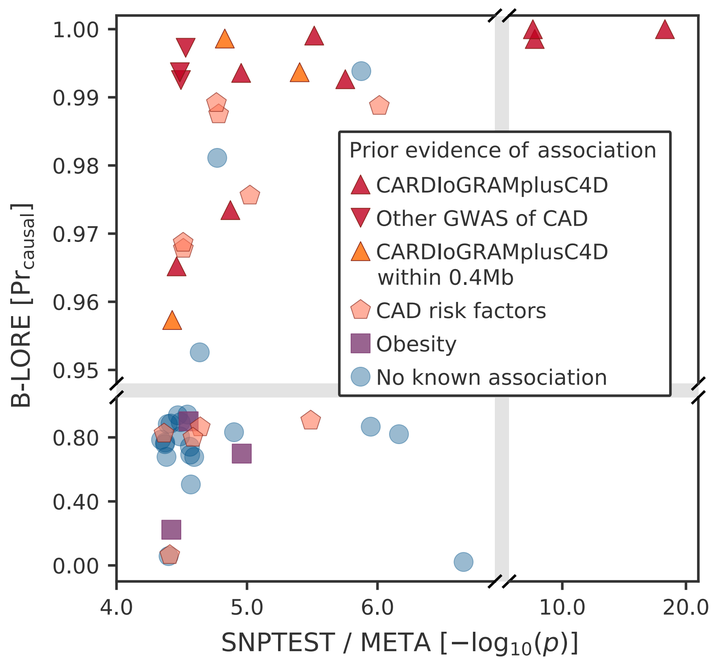
$$\begin{aligned}\mathrm{Pr}_{\text{causal}} &= p\left(\text{locus is causal} \mid \boldsymbol{\phi}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right)\\ &= 1 - p\left(\mathbf{z} = 0 \mid \boldsymbol{\phi}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right)\end{aligned}$$

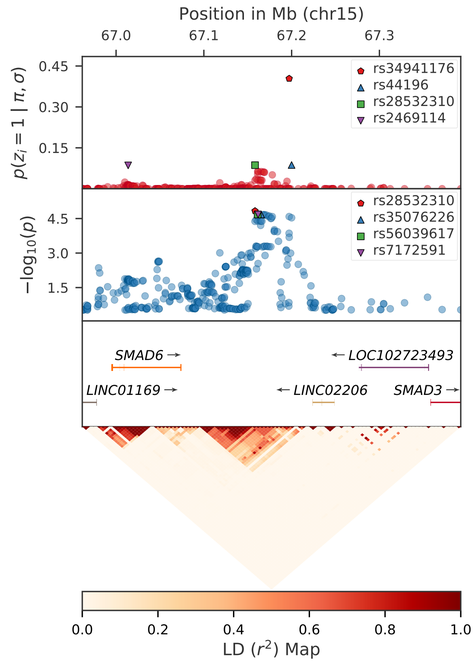
Statistical finemapping of causal variants.

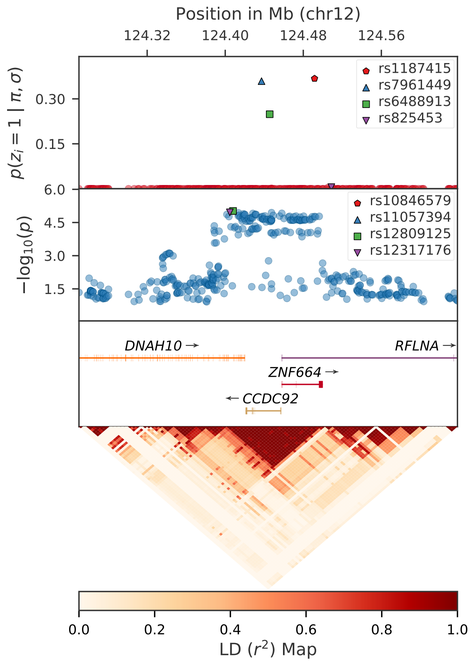
The posterior probability for SNP i to be causal is

$$p\left(z_i = 1 \mid \boldsymbol{\phi}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right)$$

5. Meta-analysis example: B-LORE discovers novel loci associated with coronary artery disease

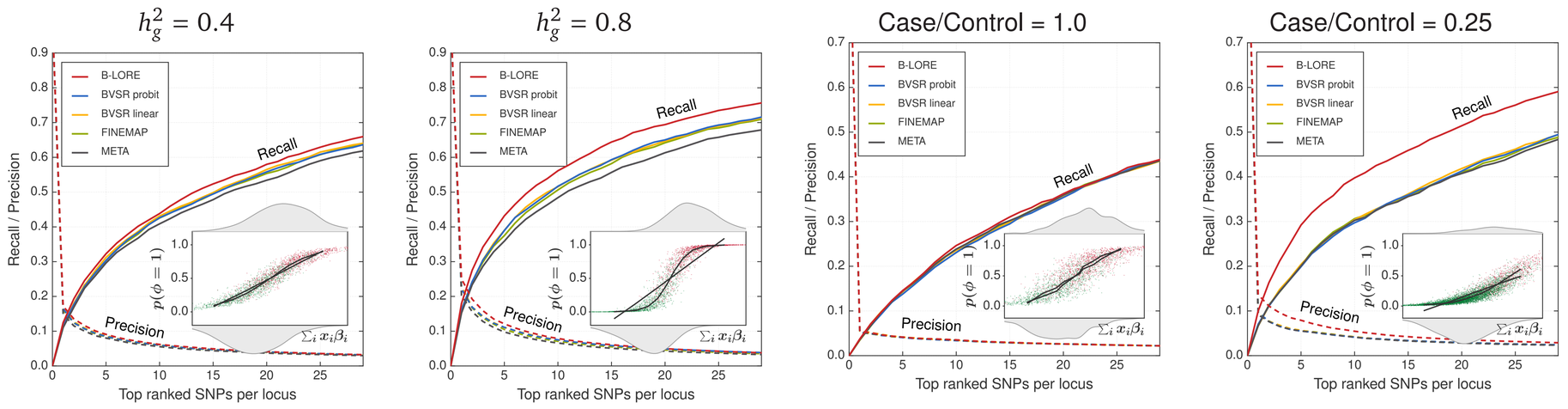






Meta-analysis of 5 cohorts, Germal Myocardial Infarction Family Studies (GerMIFS I-V) – 6234 cases and 6848 controls.

6. Examples of non-linear regimes in case-control GWAS



7. References

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8. Acknowledgement

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GEFÖRDERT VOM
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