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

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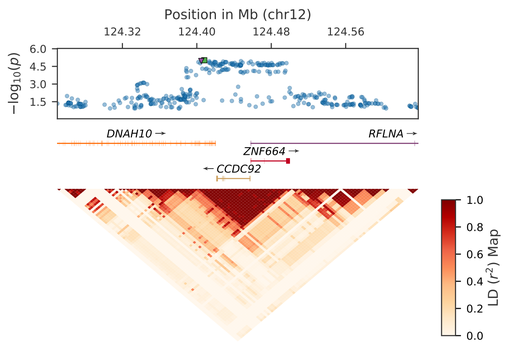
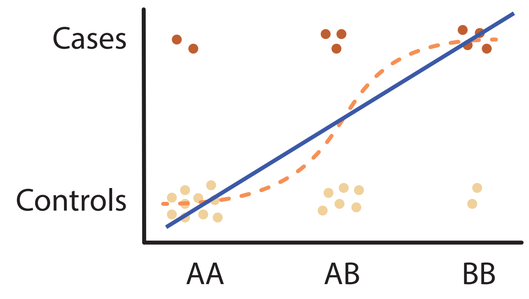
https://github.com/soedinglab/b-lore

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



Linkage disequilibrium ☹



Linear model ☹

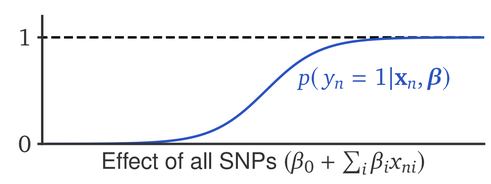
Challenges for using multiple logistic regression:

- 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 single genome-wide significant locus (cannot prioritize loci).

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,

$$p\left(\beta_i \mid \pi, \sigma\right)$$

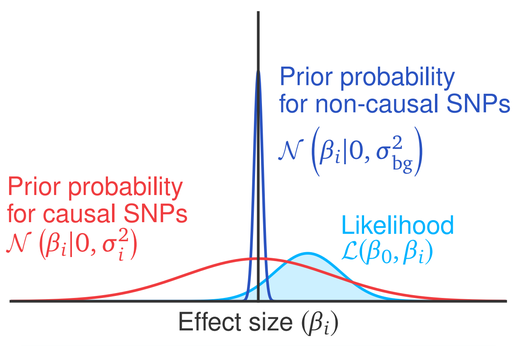
$$= \overbrace{\pi\,\mathcal{N}\left(\beta_i \mid 0, \sigma^2\right)}^{\text{Causal}} + \overbrace{(1-\pi)\,\delta_0}^{\text{Non-causal}}$$

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

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

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. Latex equation plate

$$\left(\tilde{\sigma}, \tilde{\boldsymbol{\beta}}, \tilde{\boldsymbol{\Lambda}}\right)$$

$$p\left(z_i = 1 \mid \mathbf{y}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right) = \sum_{\mathbf{z}:z_i=1} p\left(\mathbf{z} \mid \mathbf{y}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right)$$

$$\mathcal{L}(\pi, \sigma) = D' \sum_{\mathbf{z}} p\left(\mathbf{z} \mid \pi, \sigma\right) \frac{\exp\left(\frac{1}{2}\boldsymbol{\beta}_{\mathbf{z}}^{\mathsf{T}}\boldsymbol{\Lambda}_{\mathbf{z}}\boldsymbol{\beta}_{\mathbf{z}}\right)}{|\boldsymbol{\Lambda}_{\mathbf{z}}|^{\frac{1}{2}}\,|\mathrm{diag}\left(\boldsymbol{\sigma}^2_{\mathbf{z}}\right)|^{\frac{1}{2}}}$$

$$\boldsymbol{\Lambda}_{\mathbf{z}} \triangleq \tilde{\boldsymbol{\Lambda}} + \mathrm{diag}\left(\frac{1}{\boldsymbol{\sigma}^2_{\mathbf{z}}}\right) - \frac{1}{\tilde{\sigma}^2}\mathbb{I}$$

$$\boldsymbol{\beta}_{\mathbf{z}} \triangleq \boldsymbol{\Lambda}_{\mathbf{z}}^{-1}\tilde{\boldsymbol{\Lambda}}\tilde{\boldsymbol{\beta}}$$

$$\tilde{\sigma} \leftarrow \arg\max_{\sigma}\ \mathcal{L}(\pi = 1, \sigma)$$

$$\tilde{\boldsymbol{\beta}} \leftarrow \arg\max_{\boldsymbol{\beta}} \left(\log p\left(\mathbf{y} \mid \mathbf{X}, \boldsymbol{\beta}\right) + \log\mathcal{N}\left(\boldsymbol{\beta} \mid \mathbf{0},\ \tilde{\sigma}^{\mathbf{2}}\mathbb{I}\right)\right)$$

$$\tilde{\boldsymbol{\Lambda}} = \sum_{n=1}^{N} \tilde{p}_n\left(1 - \tilde{p}_n\right)\mathbf{x}_n\mathbf{x}_n^{\mathsf{T}} + \mathrm{diag}\left(\frac{1}{\tilde{\sigma}^2}\right), \quad \tilde{p}_n = p\left(y_n = 1 \mid \mathbf{x}_n, \tilde{\boldsymbol{\beta}}\right)$$

4. Inference

Prediction of causality of each locus.

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

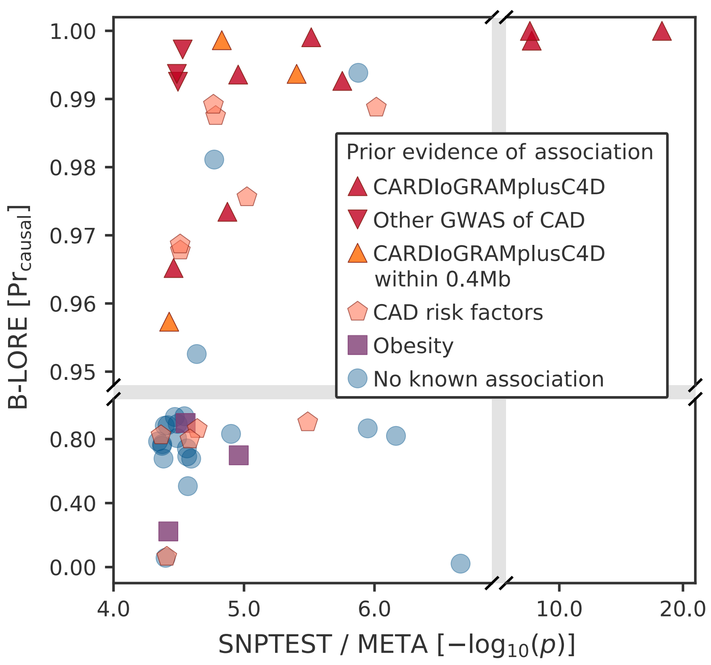
$$\begin{aligned}\mathrm{Pr}_{\text{causal}} &= p\left(\text{locus is causal} \mid \mathbf{y}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right) \\ &= 1 - p\left(\mathbf{z} = 0 \mid \mathbf{y}, \mathbf{X}, \hat{\pi}, \hat{\sigma}\right)\end{aligned}$$

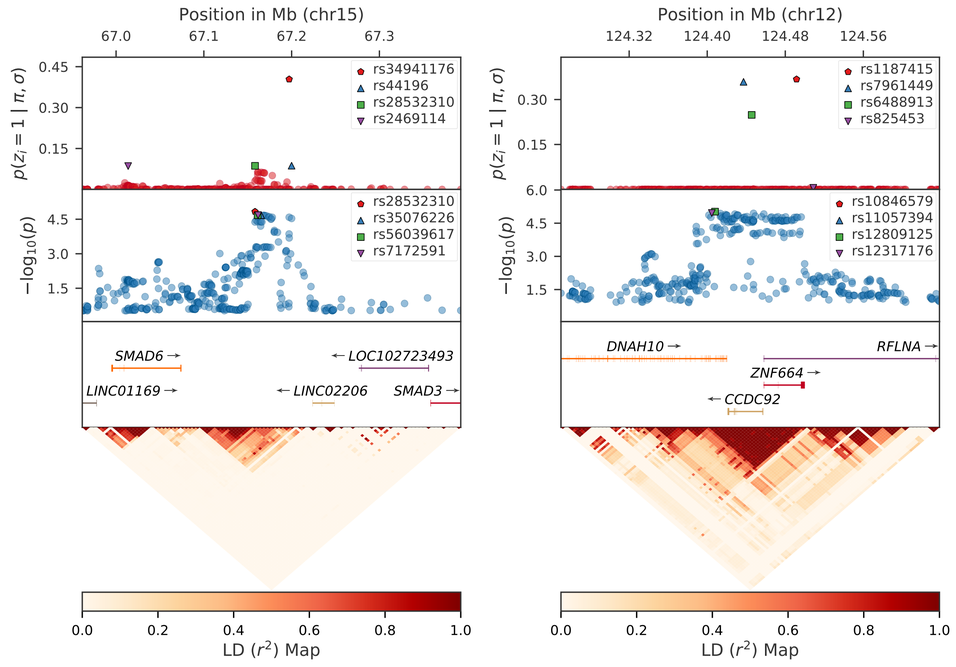
Statistical finemapping of causal variants.

The posterior probability for SNP i to be causal is

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

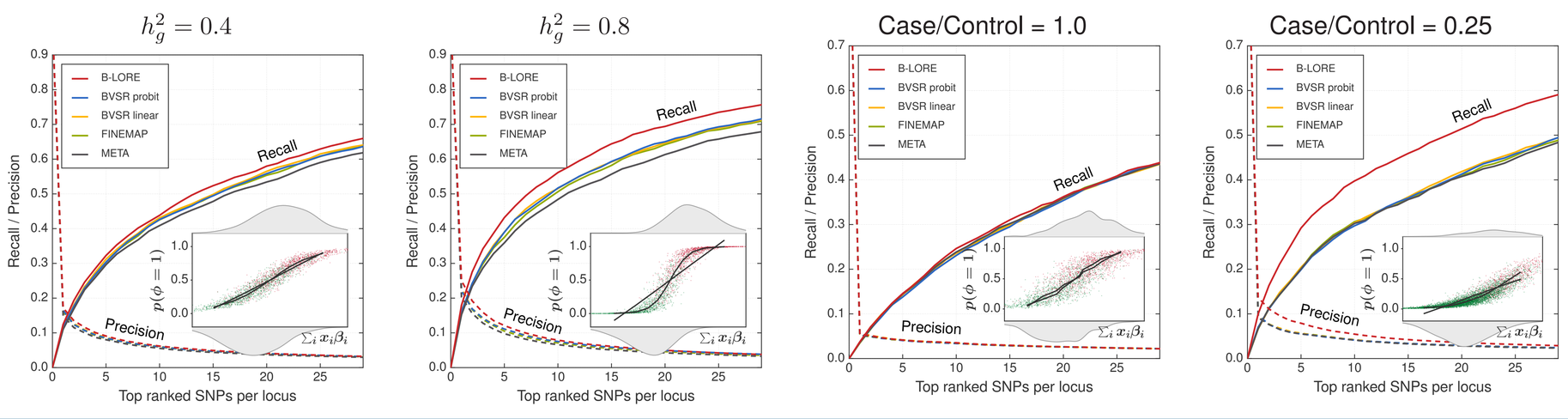
5. Meta-analysis example: B-LORE discovers novel loci associated with coronary artery disease





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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