

Bayesian variable selection logistic regression: multivariate metaanalysis in GWAS

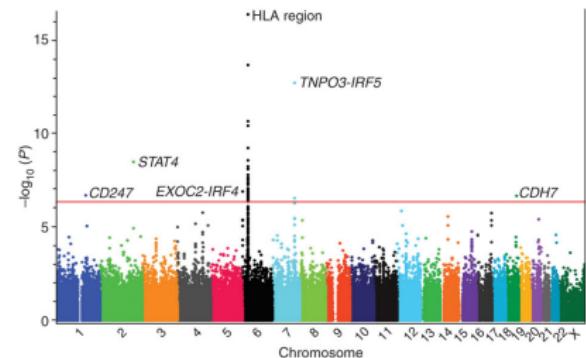
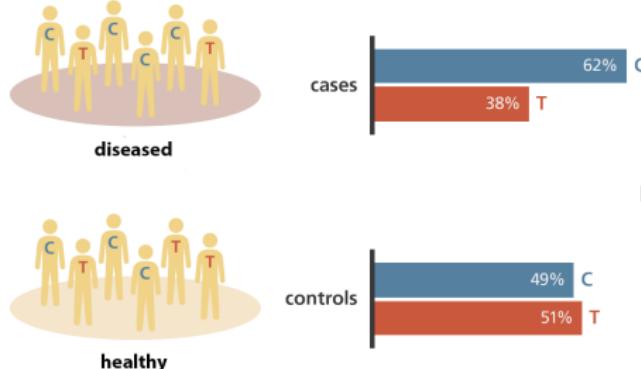
S. Banerjee & J. Söding

Max Planck Institute for Biophysical Chemistry

FEBRUARY 16, 2017



Genome-wide association studies (GWAS)



- ▶ Discovered thousands of variants associated with complex diseases

Association tests in GWAS

# of samples	Genotype (x)						Phenotype
	..	GA	TT	AT	GC	AC	..
..	GG	TT	AT	GG	AA	..	y_2
..	AA	TT	AA	GC	AA	..	y_3
..	GA	TC	AT	GC	CC	..	y_4
..	GG	TT	AT	CC	AC	..	y_5
..	AA	TC	TT	CC	AC	..	y_6

Association tests in GWAS

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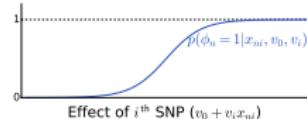
$$y_n = v_0 + v_i x_{ni} + \epsilon, \quad \text{with} \quad \epsilon \sim \mathcal{N}(0, \sigma^2) \quad \text{Quantitative phenotype}$$

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$$p(y_n = 1 | x_{ni}, v_0, v_i) = \text{lf}(v_0 + v_i x_{ni}) \quad \text{Binary phenotype}$$



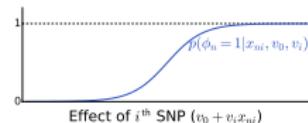
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- ▶ Is the coefficient v_i significantly different from 0? \Rightarrow P-values



Strengths

- Straightforward
- Computationally fast
- Conservative
- Easy to interpret

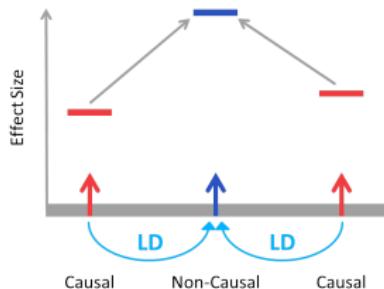
Univariate methods

Strengths

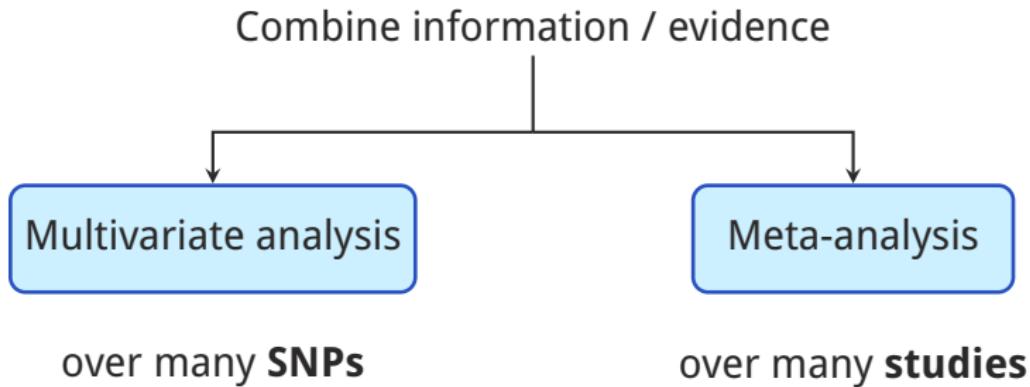
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Challenges

- Linkage disequilibrium
- Correlation vs coupling
- Genetic networks
- Low effect sizes



How GWAS have improved?

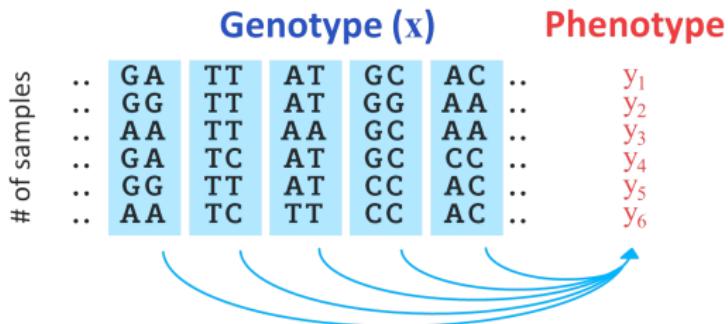


Multivariate methods

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Multivariate methods



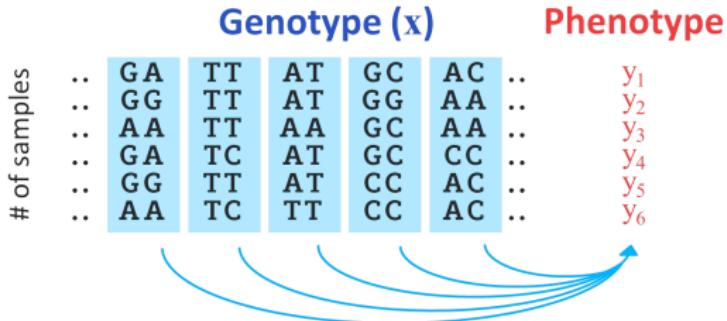
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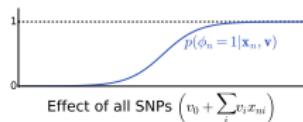
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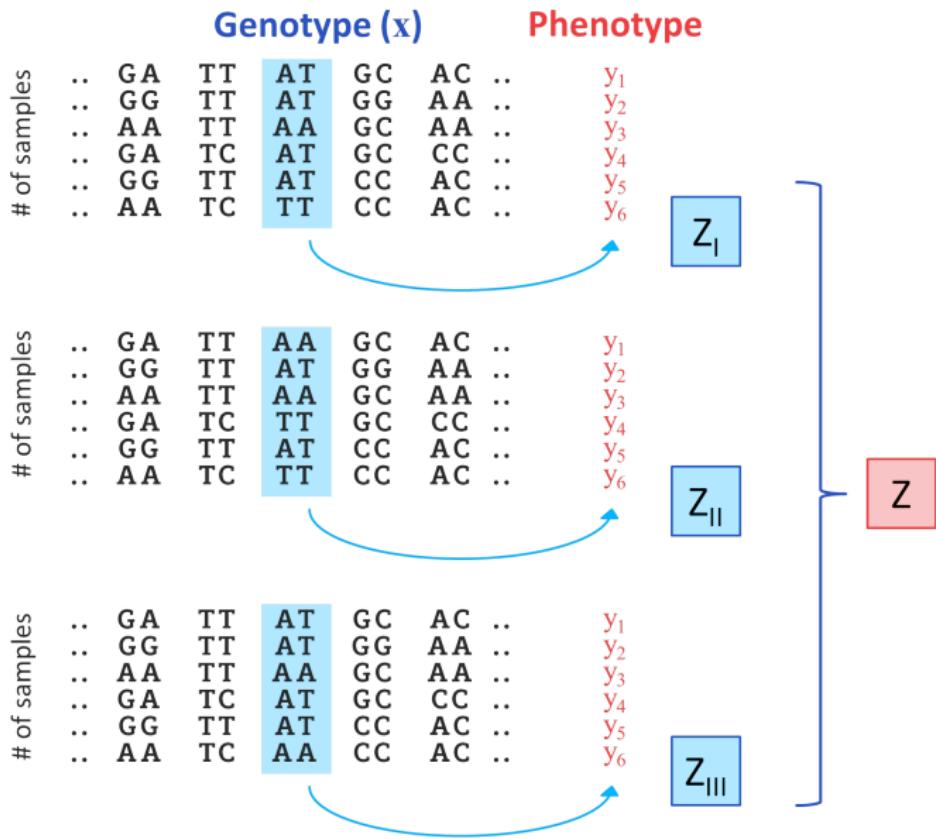


Meta-analysis

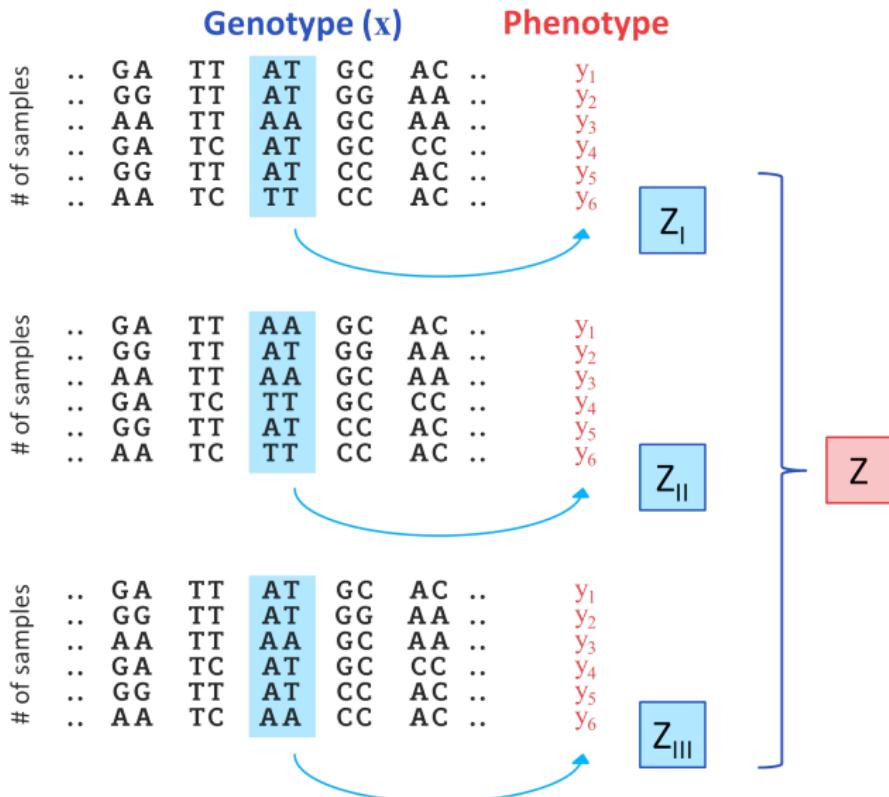
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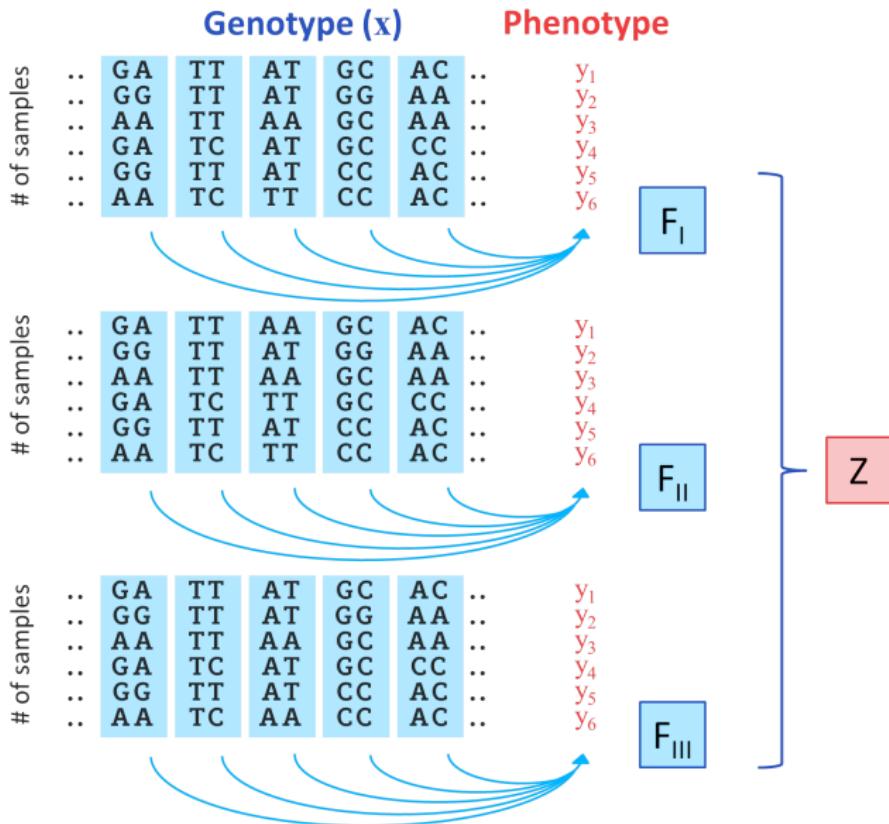
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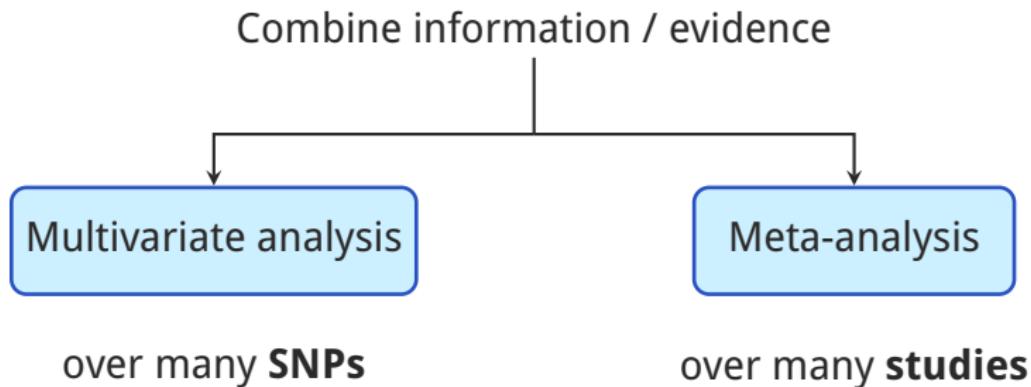
Goal of our method



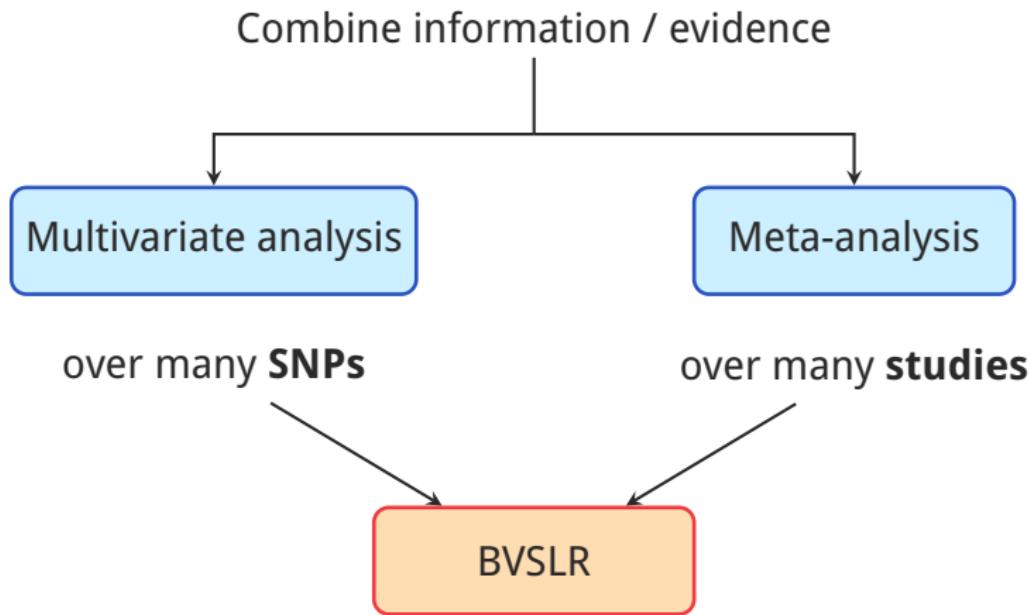
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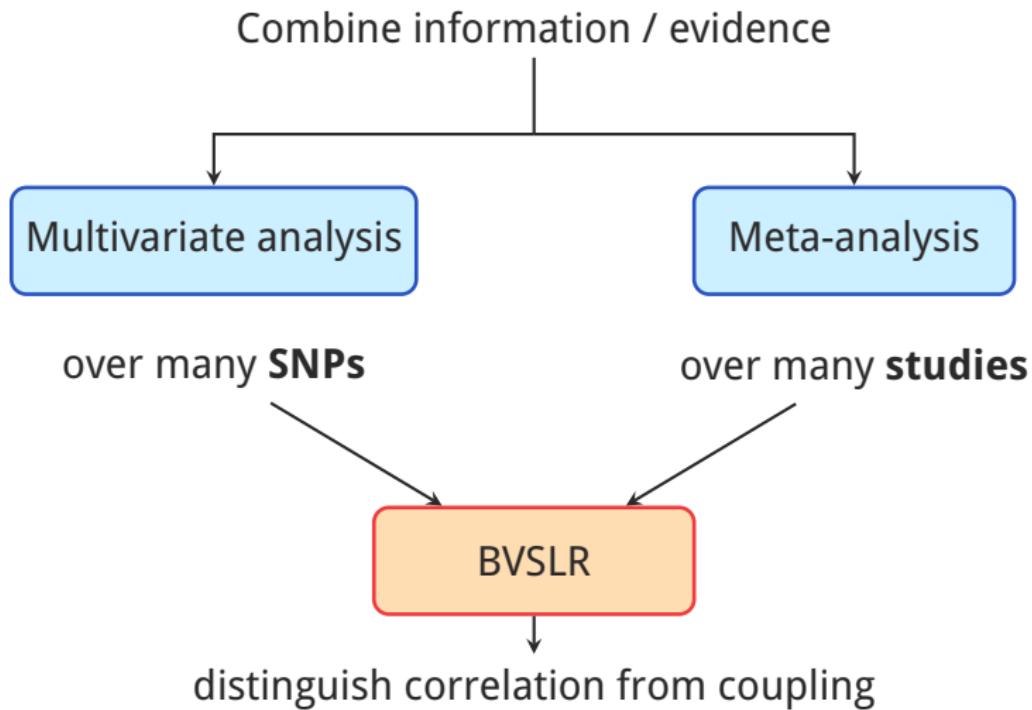
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Goal of our method



Goal of our method



Bayesian variable selection regression (BVSR)

BIMBAM

Servin and Stephens, *PLoS Genetics* 2007
Guan and Stephens, *Ann. Appl. Stats.* 2011

$$y_n = v_0 + \sum_i v_i x_{ni} + \epsilon, \quad \text{with} \quad \epsilon \sim \mathcal{N}(0, \tau^{-1}) \quad \text{Quantitative phenotype}$$

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- ▶ Likelihood for N patients:

$$p(\mathbf{y} | \mathbf{x}, \mathbf{v}, \tau) = \mathcal{N}(\mathbf{y} | \mathbf{x}^\top \mathbf{v}, \tau^{-1} \mathbb{I})$$

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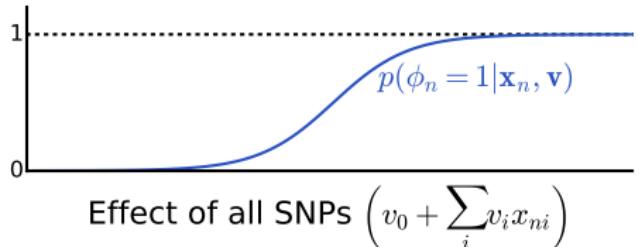
- ▶ Likelihood for N patients:

$$p(\mathbf{y} | \mathbf{x}, \mathbf{v}, \tau) = \mathcal{N}(\mathbf{y} | \mathbf{x}^T \mathbf{v}, \tau^{-1} \mathbb{I})$$

- ▶ Number of SNPs \gg samples → Overfitting
- ▶ Effective priors on \mathbf{v} for sparsity

Bayesian variable selection logistic regression (BVSLR)

$$p(\phi_n = 1 | \mathbf{x}_n, \mathbf{v}) = \text{lf}\left(v_0 + \sum_i v_i x_{ni}\right)$$

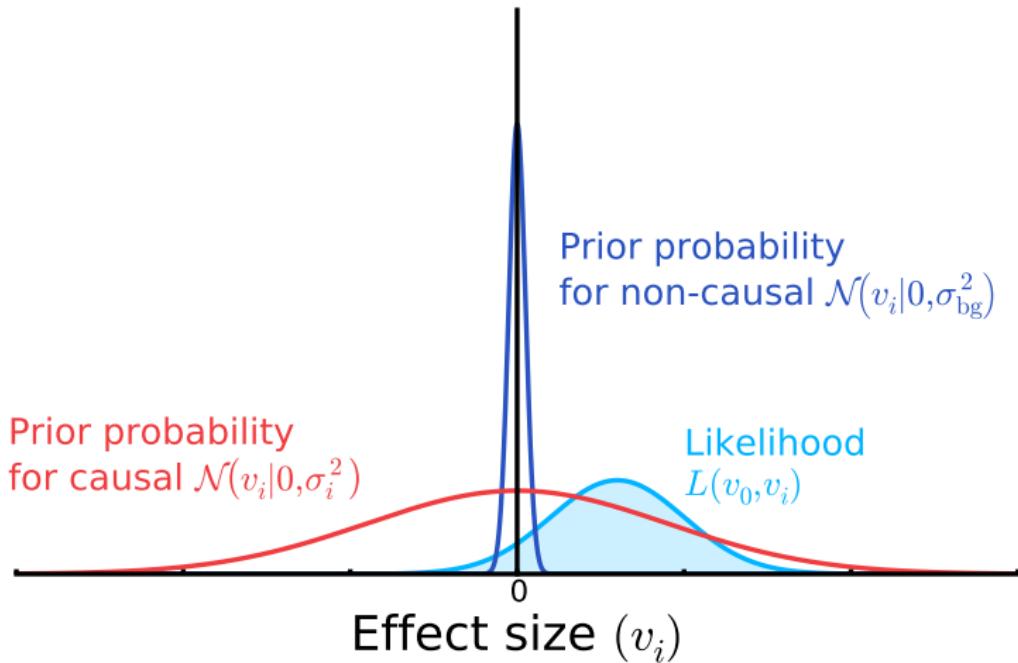


- Likelihood for N patients:

$$p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) = \prod_{n=1}^N p(\phi_n | \mathbf{x}_n, \mathbf{v}) = \prod_{n=1}^N \frac{\exp(\phi_n \mathbf{v}^\top \mathbf{x}_n)}{1 + \exp(\mathbf{v}^\top \mathbf{x}_n)}$$

Sparsity in BVSR / BVSLR

Looks at both **null hypothesis** and **alternate hypothesis**



Priors in BVSR

$$p(\mathbf{y} | \mathbf{x}, \mathbf{v}, \tau) = \mathcal{N}(\mathbf{y} | \mathbf{x}^\top \mathbf{v}, \tau^{-1} \mathbb{I})$$

$$p(\tau) = \text{Gamma}\left(\frac{\lambda}{2}, \frac{\kappa}{2}\right)$$

$$p(v_0 | \tau) = \mathcal{N}(v_0 | 0, \sigma_\mu^2 / \tau)$$

$$p(v_i | \tau) = \underbrace{(1 - \pi) \delta_0}_{\text{Non-causal}} + \underbrace{\pi \mathcal{N}(v_i | 0, \sigma_a^2 / \tau)}_{\text{Causal}}$$

Hyperparameters $\Rightarrow \lambda, \kappa, \pi, \sigma_\mu, \sigma_a$

Priors in BVSLR

$$p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) = \prod_{n=1}^N \frac{\exp(\phi_n \mathbf{v}^\top \mathbf{x}_n)}{1 + \exp(\mathbf{v}^\top \mathbf{x}_n)}$$

$$p(v_i | \boldsymbol{\theta}) = \underbrace{(1 - \pi) \mathcal{N}(v_i | 0, \sigma_{bg}^2)}_{\text{Non-causal}} + \underbrace{\pi \mathcal{N}(v_i | \mu, \sigma^2)}_{\text{Causal}}$$

Hyperparameters $\boldsymbol{\theta} \Rightarrow \pi, \mu, \sigma_{bg}, \sigma$

Causality configurations

$$\begin{aligned} p(v_i | \boldsymbol{\theta}) &= \underbrace{(1 - \pi) \mathcal{N}(v_i | 0, \sigma_{\text{bg}}^2)}_{\text{Non-causal}} + \underbrace{\pi \mathcal{N}(v_i | \mu, \sigma^2)}_{\text{Causal}} \\ &= \sum_{z_i=0,1} \pi^{z_i} (1 - \pi)^{(1-z_i)} \mathcal{N}(v_i | \mu_{\mathbf{z},i}, \sigma_{\mathbf{z},i}^2) \\ \mu_{\mathbf{z},i} &= z_i \mu \quad \text{and} \quad \sigma_{\mathbf{z},i}^2 = \sigma_{\text{bg}}^2 + z_i [\sigma^2 - \sigma_{\text{bg}}^2] \end{aligned}$$

$\mathbf{z} \in \{0,1\}^I \Rightarrow \text{Causality configurations}$

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

Broad overview of BVSLR

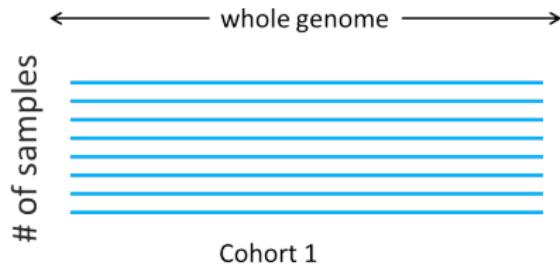
- ▶ Learn the hyperparameters (θ) from the data
- ▶ The posterior probability for SNP i to be causal is

$$p(z_i = 1 | \phi, \mathbf{x}, \theta) = \sum_{\mathbf{z}: z_i = 1} p(\mathbf{z} | \phi, \mathbf{x}, \theta)$$

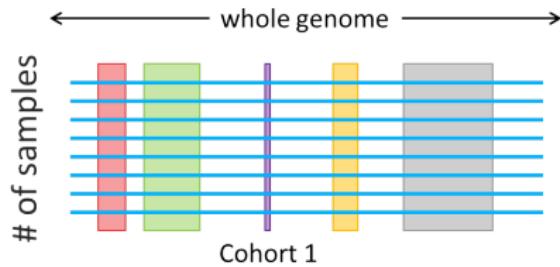
- ▶ The probability for a locus to be causal = 1 – probability of *not* having a single causal SNP

$$p(\text{locus is causal} | \phi, \mathbf{x}, \theta) = 1 - p(\mathbf{z} = \mathbf{0} | \phi, \mathbf{x}, \theta)$$

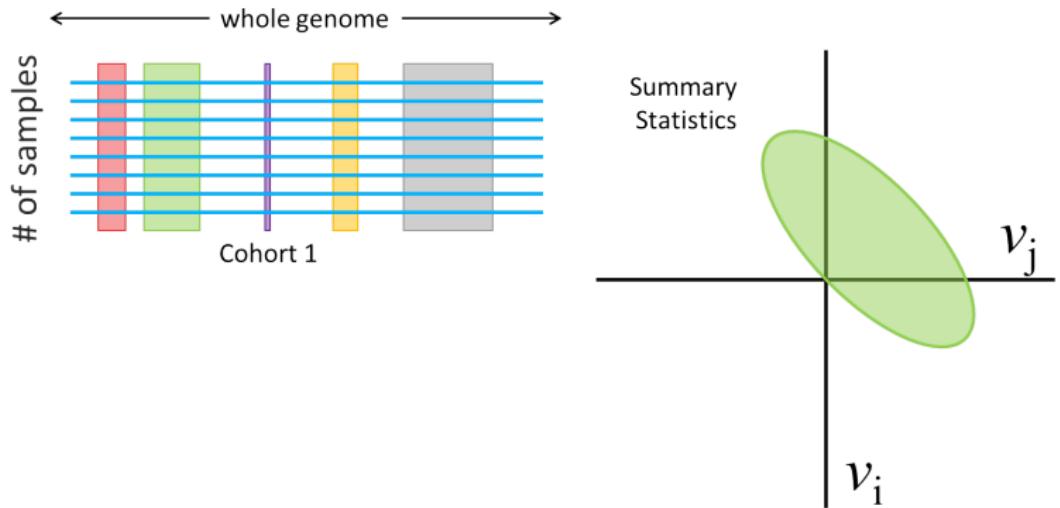
BVSLR can be extended to multiple studies



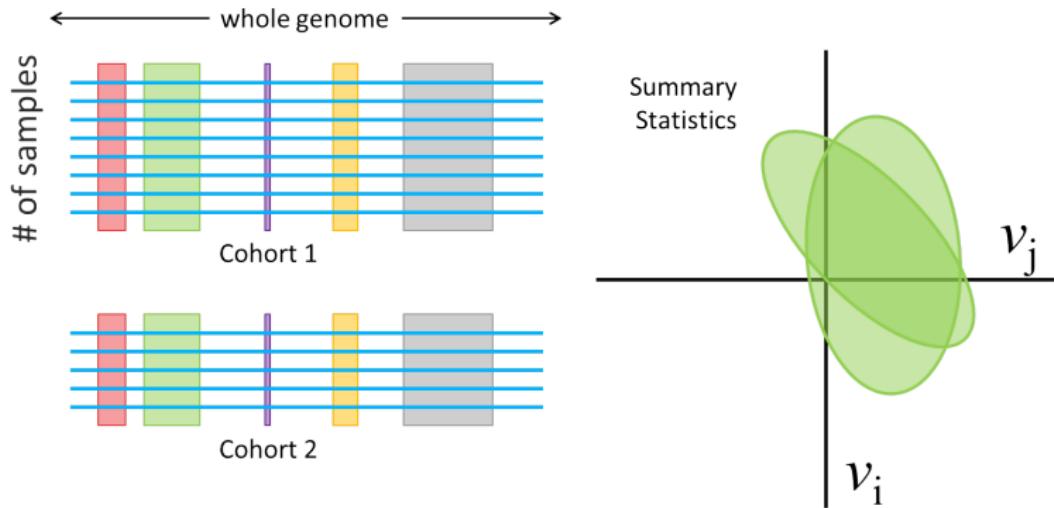
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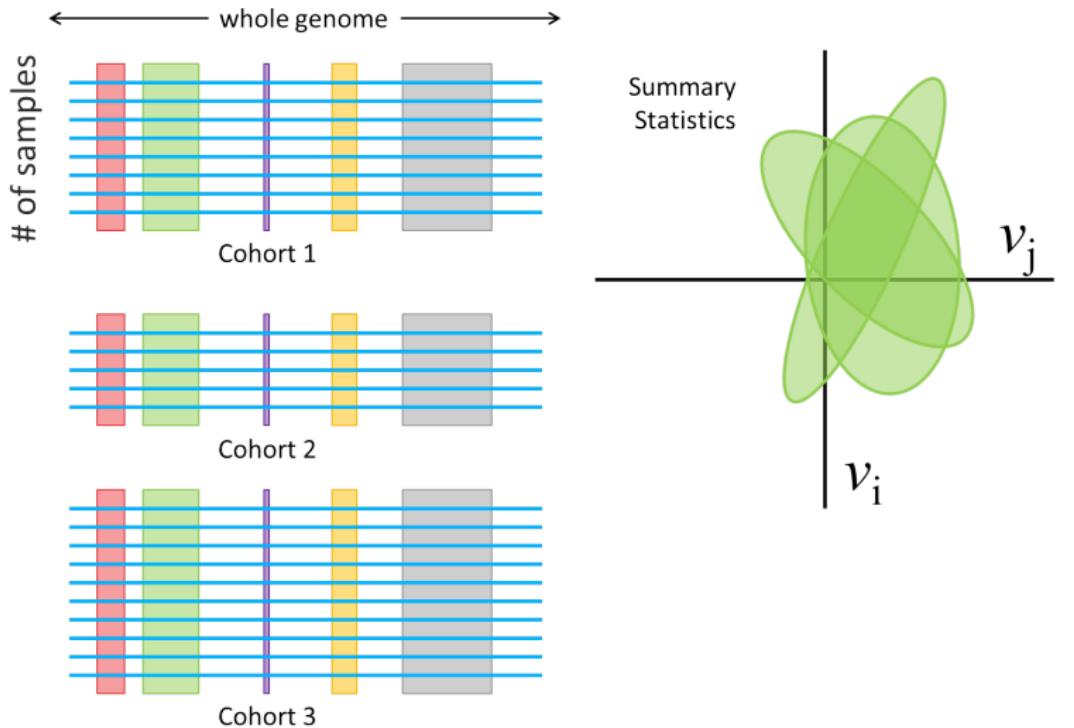
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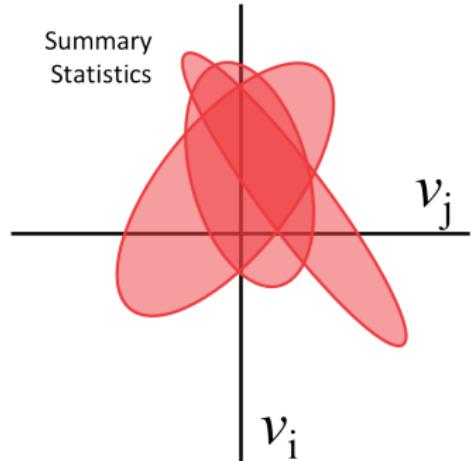
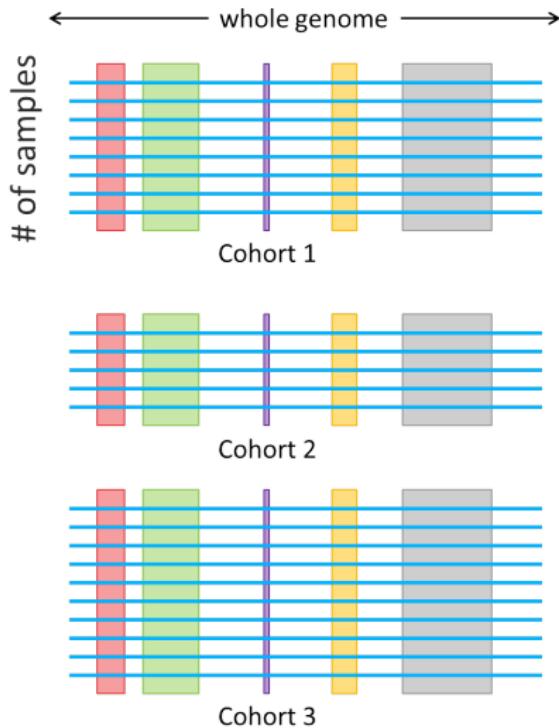
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BVSLR can be extended to multiple studies



Simulation details

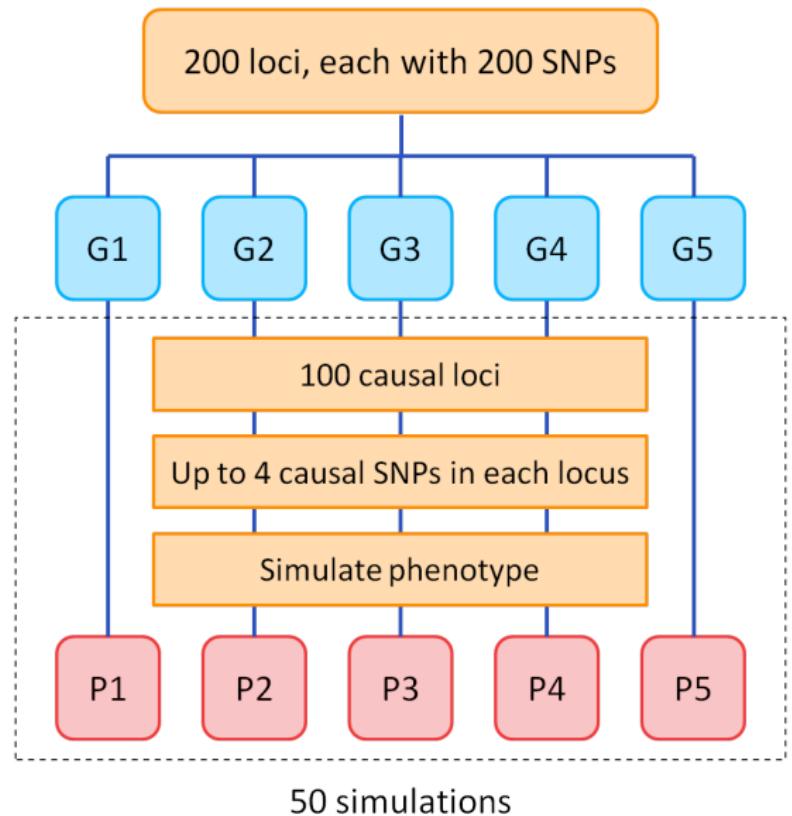
- ▶ Genotype: German Myocardial Infarction Family Study (GERMIFS)
- ▶ Five cohorts : G1, G2, G3, G4, G5
- ▶ Phenotype simulation:

$$\text{Disease liability} \quad Y_n = \sum_i v_i x_{ni} + \varepsilon_n$$

$$\text{Var}\left(\sum_i v_i x_{ni}\right) = h_g^2 = 0.4 \text{ and } \text{Var}(\varepsilon) = 0.6$$

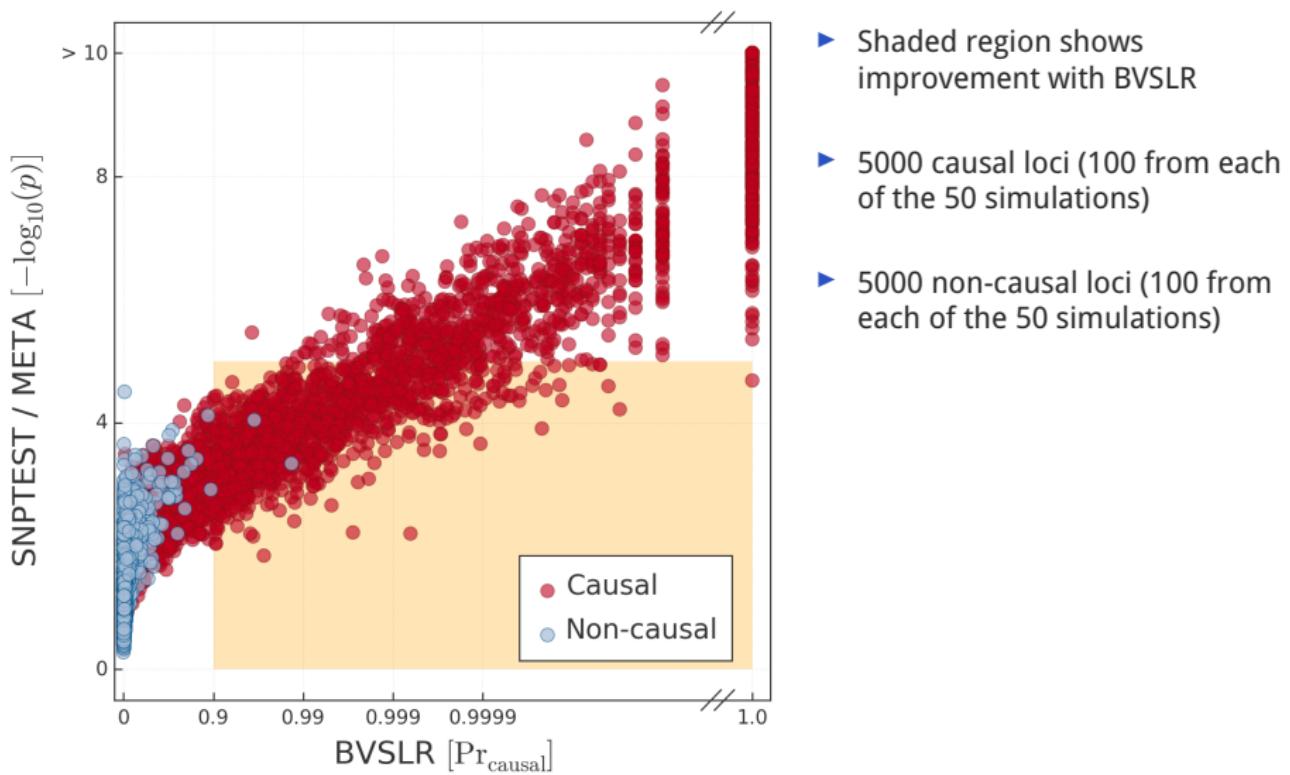
Cases are sampled from Y_n exceeding the threshold of normal distribution truncating the proportion of k (disease prevalence)

Simulation details

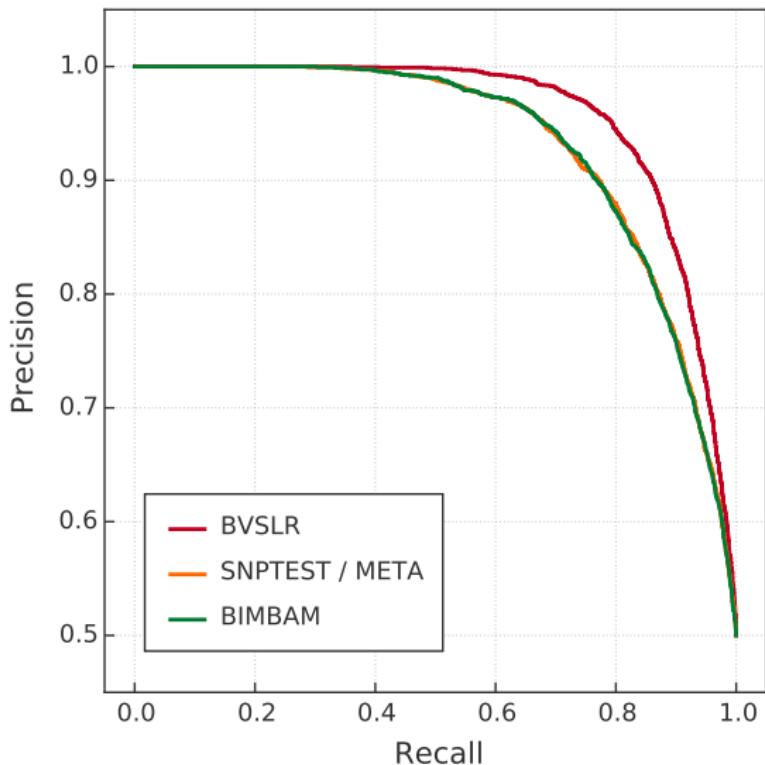


- ▶ BVSLR
- ▶ BIMBAM
- ▶ SNPTEST / META
- ▶ PAINTOR

Prediction of causal loci

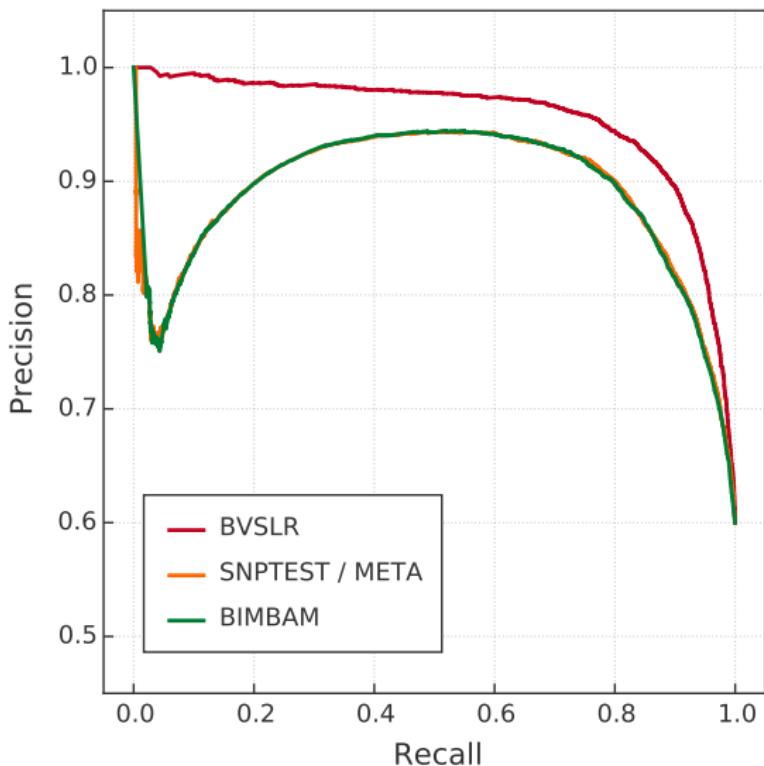


Prediction of causal loci



$$\text{Precision} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$
$$\text{Recall} = \frac{\text{TP}}{\text{TP} + \text{FN}}$$

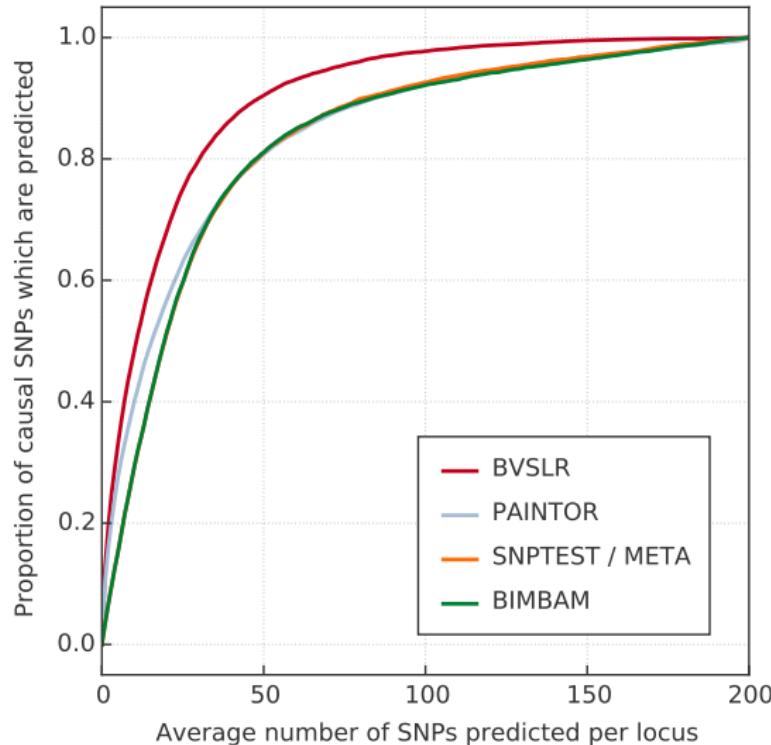
Correlation vs coupling



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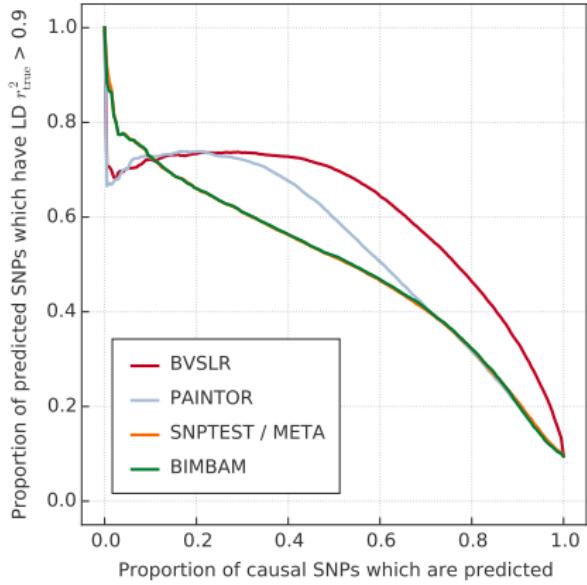
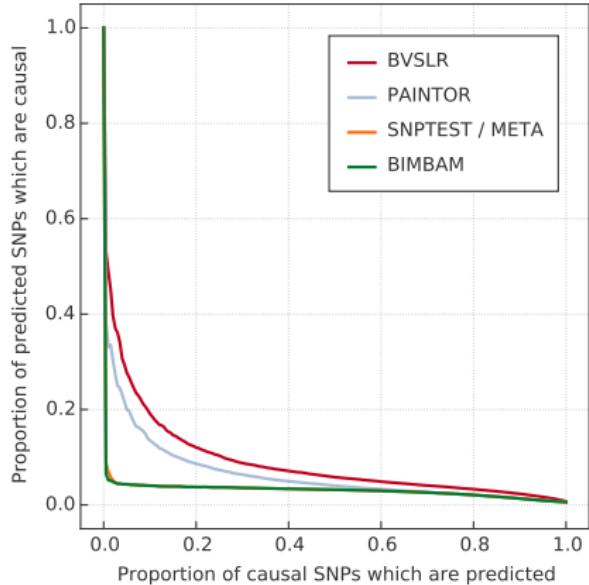
- ▶ 8 loci (out of 200) in LD with each other were introduced in the simulation
- ▶ Non-causal loci in correlation with multiple causal loci reduces precision of SNPTEST

Finemapping causal variants



► Comparable to PAINTOR up to 20% recall

BVSLR predicts SNPs in strong LD with actual ones



Challenges of BVSLR

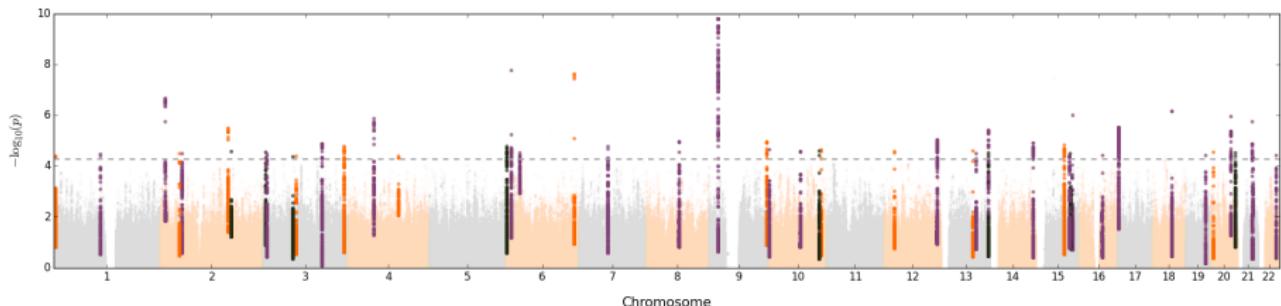
- ▶ Computational time (summing over z-states)
- ▶ New summary statistics
- ▶ Assumes underlying data *must* have sufficient causal and non-causal SNPs

Association with coronary artery diseases (CAD)

- ▶ 5 GERMIFS cohorts
- ▶ 6228 cases, 6854 controls
- ▶ Imputed with 1000G Phase 1

Association with coronary artery diseases (CAD)

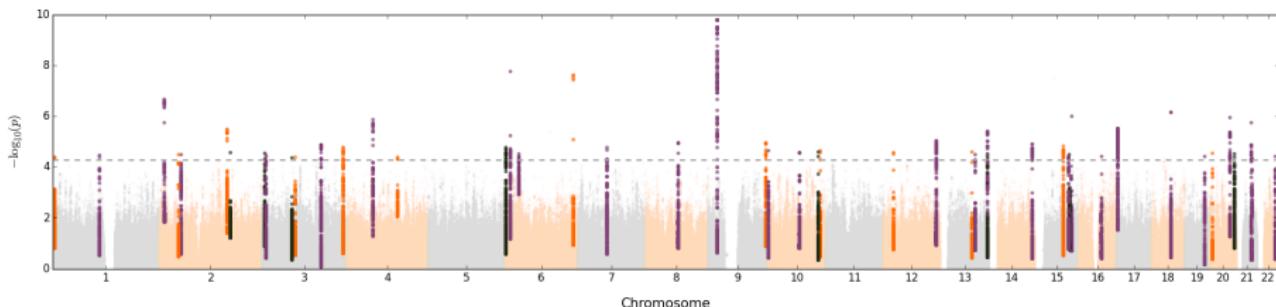
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GWAS using SNPTEST / META

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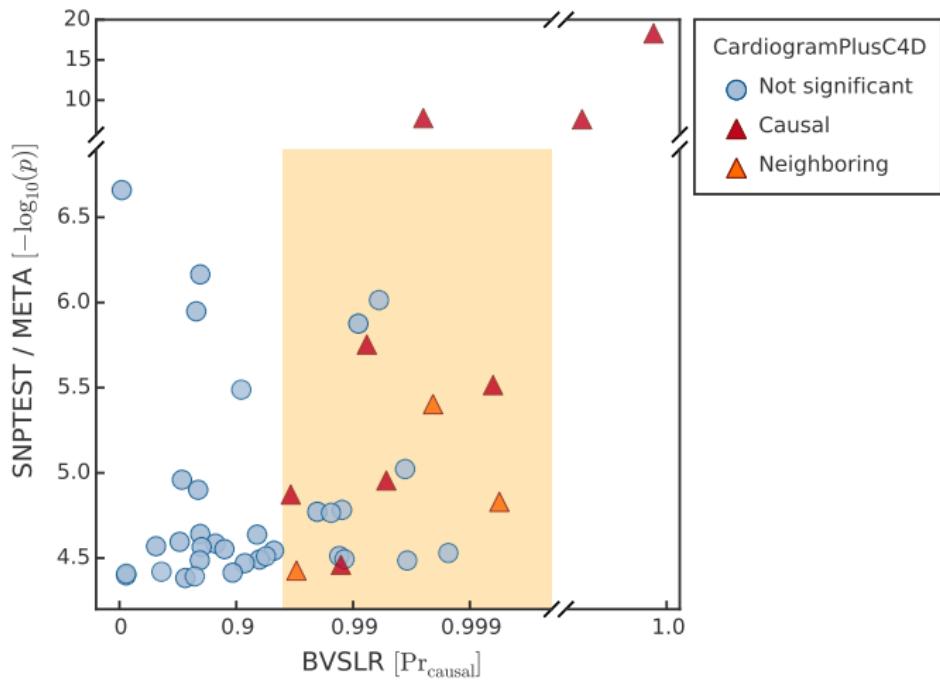
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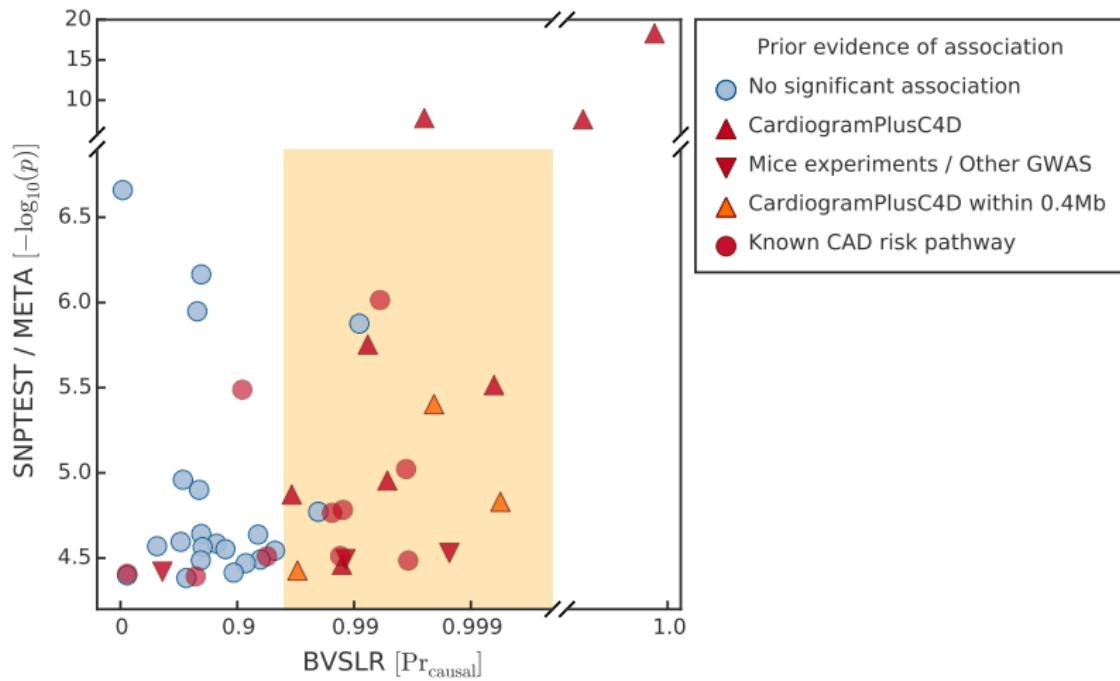
GWAS using SNPTEST / META

- ▶ Applied BVSLR on these 45 loci, selecting 400 SNPs at each locus.

BVSLR predictions



BVSLR predictions

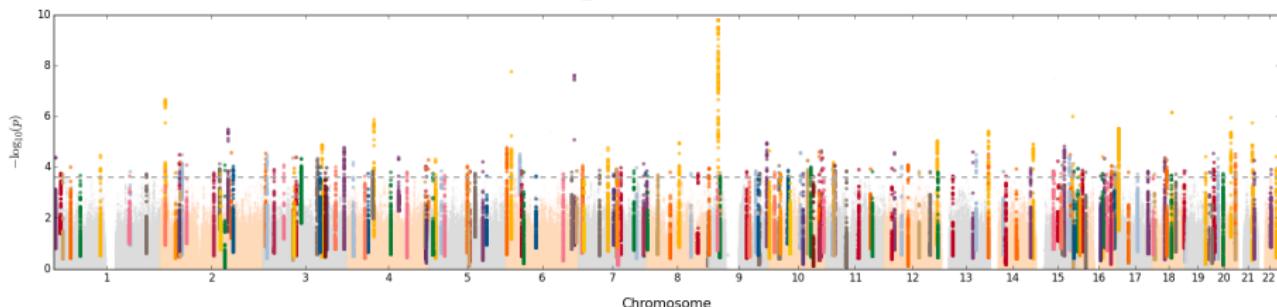


Top BVSLR predicted loci (not discovered in CardiogramPlusC4D)

Region	Pr	Gene	Comments
6p21.3	0.998	C6orf10-BTNL2	GWAS for CAD in Han Chinese, 2012
15q25	0.997	IL-16	GWAS for CAD in Han Chinese, 2012
4q13.1	0.996	desert	-
15q25	0.994	AKAP13	C. hypertrophy (mice) / GWAS (BP in Koreans, 2011)
2p16	0.994	NRXN1	GWAS for CAD in OHGS1 + WTCCC2
3q28	0.992	IL1RAP	Involved in risk pathway
6p25	0.992	SERPINB	patented as biomarker for CVD
20q13.3	0.991	EDN3	GWAS hit for BP / CVD
7q11.22	0.990	AUTS2	-
12q24	0.982	ZNF664	GWAS hit for HDL-C, TG
13q21.1	0.981	ARHGEF1	Controls vascular tone and BP

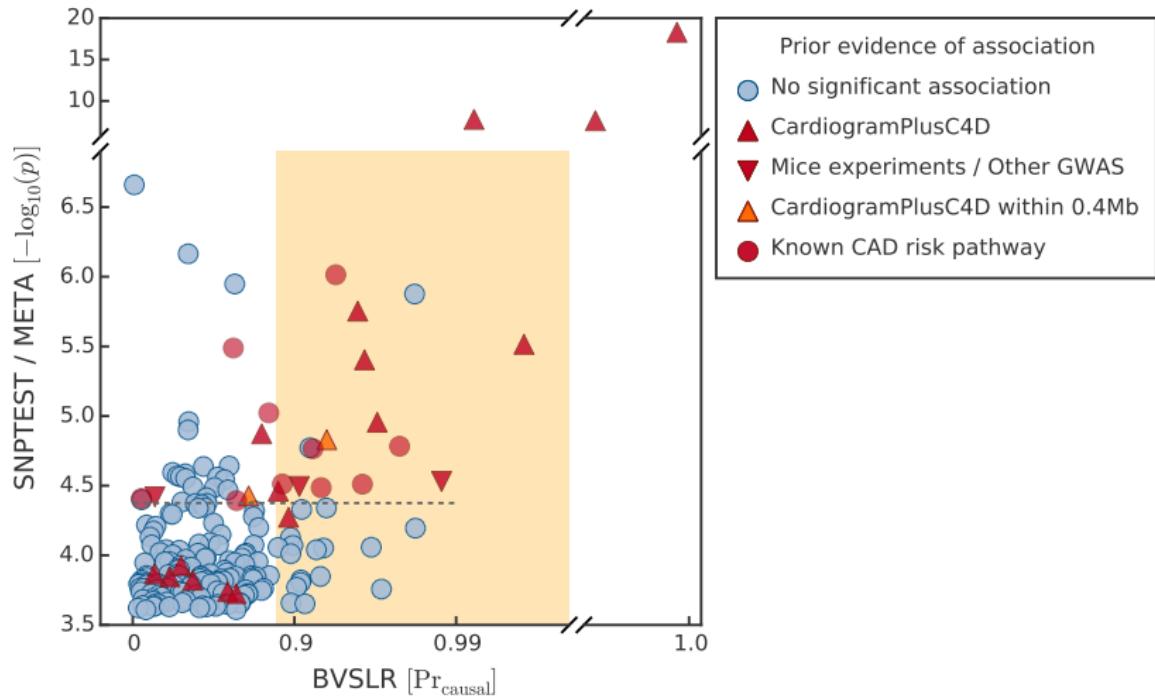
Extension to 200 loci

GWAS using SNPTEST / META



- ▶ Applied BVSLR on these 200 loci, selecting 400 SNPs at each locus.

Extension to 200 loci



Possible extensions of BVSLR

- ▶ Integrate additional data e.g. ENCODE, DeepSEA, etc.
- ▶ Gene-environment interaction
- ▶ Dominant and recessive models
- ▶ Integration with GTEx

- ▶ Novel Bayesian method for GWAS
- ▶ Multivariate analysis in meta studies
- ▶ Improves precision
- ▶ Predicts new associations in CAD

Many thanks to ...



Johannes Söding

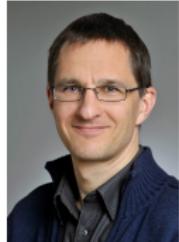


Heribert Schunkert



Jeanette Erdmann

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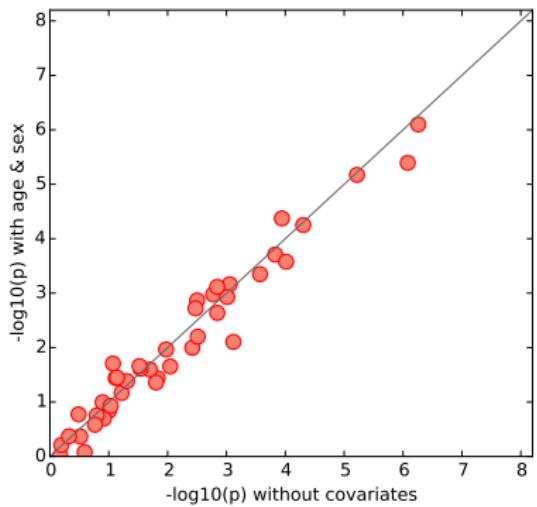


AG Söding

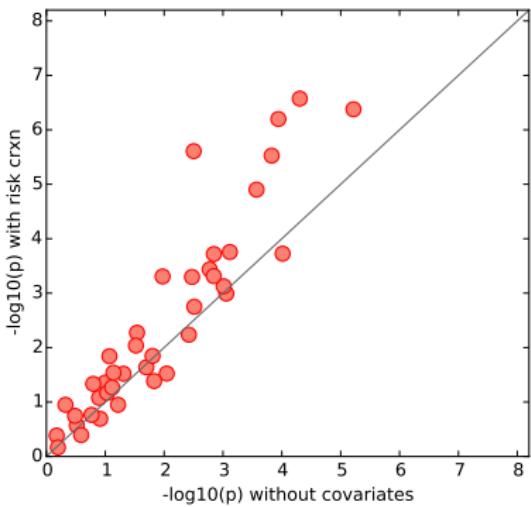
Thank you!

Risk correction can be improved

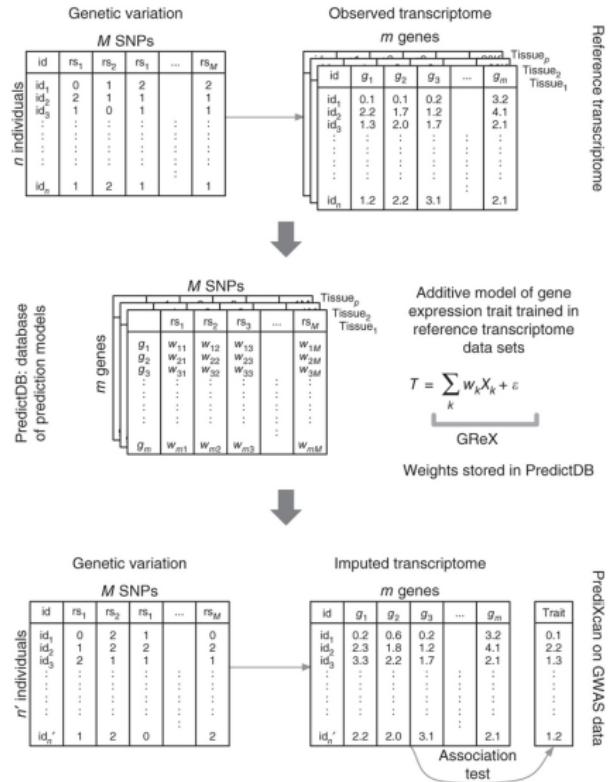
Pirinen *et al.*, Nat. Gen. 2012



Liability correction

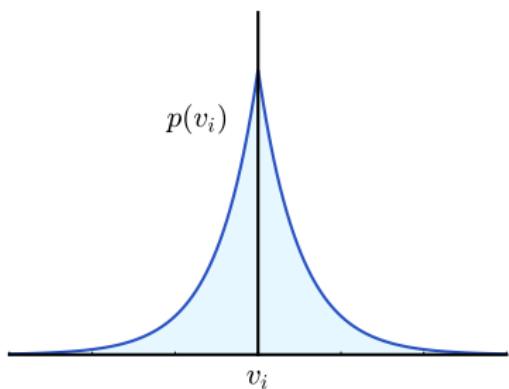


Integration with GTEx



LASSO penalisation

- ▶ Constraint: $\sum_i |v_i| \leq t$, where $t(> 0)$ is a *tuning parameter*.
- ▶ Applied as a Lagrangian penalty to the joint log-likelihood.



LASSO penalty assumes implicit Laplace prior \rightarrow more zero-valued coefficients.

Problems:

- ▶ Multicollinearity
- ▶ Variability in penalty parameter

Optimising the hyperparameters

$$p(v_i | \theta) = \sum_{z_i=0,1} \pi^{z_i} (1-\pi)^{(1-z_i)} \mathcal{N}(v_i | \mu_{\mathbf{z},i}, \sigma_{\mathbf{z},i}^2)$$

Optimising the hyperparameters

$$p(v_i | \boldsymbol{\theta}) = \sum_{z_i=0,1} \pi^{z_i} (1-\pi)^{(1-z_i)} \mathcal{N}(v_i | \mu_{\mathbf{z},i}, \sigma_{\mathbf{z},i}^2)$$

$$p(\mathbf{v} | \boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))$$

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$$p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) = \prod_{n=1}^N \frac{\exp(\phi_n \mathbf{v}^\top \mathbf{x}_n)}{1 + \exp(\mathbf{v}^\top \mathbf{x}_n)}$$

Optimising the hyperparameters

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Evidence approximation: Maximising the marginal likelihood

$$\begin{aligned} mL(\boldsymbol{\theta}) &= p(\boldsymbol{\phi} | \mathbf{x}, \boldsymbol{\theta}) \\ &= \int p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) p(\mathbf{v} | \boldsymbol{\theta}) d\mathbf{v} \rightarrow \max \end{aligned}$$

$$mL(\boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \int p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2)) d\mathbf{v}$$

Optimising the hyperparameters

$$p(\mathbf{v} | \boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))$$

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Laplace approximation (?)

Optimising the hyperparameters

$$p(\mathbf{v} | \boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))$$

$$p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) = \prod_{n=1}^N \frac{\exp(\phi_n \mathbf{v}^\top \mathbf{x}_n)}{1 + \exp(\mathbf{v}^\top \mathbf{x}_n)}$$

Evidence approximation: Maximising the marginal likelihood

$$\begin{aligned} mL(\boldsymbol{\theta}) &= p(\boldsymbol{\phi} | \mathbf{x}, \boldsymbol{\theta}) \\ &= \int p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) p(\mathbf{v} | \boldsymbol{\theta}) d\mathbf{v} \rightarrow \max \end{aligned}$$

$$mL(\boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \int p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2)) d\mathbf{v}$$

Laplace approximation (?)

Quasi-Laplace approximation

$$mL(\boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \int p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2)) d\mathbf{v}$$
$$p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))$$
$$= p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \tilde{\boldsymbol{\mu}}, \text{diag}(\tilde{\boldsymbol{\sigma}}^2)) \times \frac{\mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))}{\mathcal{N}(\mathbf{v} | \tilde{\boldsymbol{\mu}}, \text{diag}(\tilde{\boldsymbol{\sigma}}^2))}$$
$$\propto \mathcal{N}(\mathbf{v} | \tilde{\boldsymbol{\mu}}, \tilde{\boldsymbol{\sigma}}^2)$$

Quasi-Laplace approximation

$$mL(\boldsymbol{\theta}) = \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \int p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2)) d\mathbf{v}$$
$$p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))$$
$$= \underbrace{p(\boldsymbol{\phi} | \mathbf{x}, \mathbf{v}) \mathcal{N}(\mathbf{v} | \tilde{\boldsymbol{\mu}}, \text{diag}(\tilde{\boldsymbol{\sigma}}^2))}_{\propto \mathcal{N}(\mathbf{v} | \tilde{\mathbf{v}}, \tilde{\boldsymbol{\Lambda}}^{-1})} \times \frac{\mathcal{N}(\mathbf{v} | \boldsymbol{\mu}_{\mathbf{z}}, \text{diag}(\boldsymbol{\sigma}_{\mathbf{z}}^2))}{\mathcal{N}(\mathbf{v} | \tilde{\boldsymbol{\mu}}, \text{diag}(\tilde{\boldsymbol{\sigma}}^2))}$$

Analytical solution

$$mL(\boldsymbol{\theta}) = p(\boldsymbol{\phi} | \mathbf{x}, \boldsymbol{\theta})$$

$$\approx D' \sum_{\mathbf{z}} p(\mathbf{z} | \boldsymbol{\theta}) \frac{|\text{diag}(\boldsymbol{\lambda}_{\mathbf{z}})|^{\frac{1}{2}}}{|\boldsymbol{\Lambda}_{\mathbf{z}}|^{\frac{1}{2}}} \exp \left(-\frac{1}{2} \boldsymbol{\mu}_{\mathbf{z}}^\top \text{diag}(\boldsymbol{\lambda}_{\mathbf{z}}) \boldsymbol{\mu}_{\mathbf{z}} + \frac{1}{2} \mathbf{v}_{\mathbf{z}}^\top \boldsymbol{\Lambda}_{\mathbf{z}} \mathbf{v}_{\mathbf{z}} \right)$$

where

$$\boldsymbol{\Lambda}_{\mathbf{z}} := \tilde{\boldsymbol{\Lambda}} - \text{diag}(\tilde{\boldsymbol{\lambda}}) + \text{diag}(\boldsymbol{\lambda}_{\mathbf{z}})$$

$$\mathbf{v}_{\mathbf{z}} := \boldsymbol{\Lambda}_{\mathbf{z}}^{-1} [\tilde{\boldsymbol{\Lambda}} \tilde{\mathbf{v}} + \text{diag}(\boldsymbol{\lambda}_{\mathbf{z}}) \boldsymbol{\mu}_{\mathbf{z}} - \text{diag}(\tilde{\boldsymbol{\lambda}}) \tilde{\boldsymbol{\mu}}]$$

- ▶ Optimization can be done by gradient descent methods (e.g. L-BFGS).

Inference of causality in BVSLR

Using the definition of conditional probability,

$$p(\mathbf{z} | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta}) = \frac{p(\boldsymbol{\phi}, \mathbf{z} | \mathbf{x}, \boldsymbol{\theta})}{p(\boldsymbol{\phi} | \mathbf{x}, \boldsymbol{\theta})}$$

The posterior probability for SNP i to be causal is

$$p(z_i = 1 | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta}) = \sum_{\mathbf{z}: z_i = 1} p(\mathbf{z} | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta})$$

Inference of causality in BVSLR

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The posterior probability for SNP i to be causal is

$$p(z_i = 1 | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta}) = \sum_{\mathbf{z}: z_i = 1} p(\mathbf{z} | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta})$$

The probability for a locus to be causal = 1 – probability of *not* having a single causal SNP

$$p(\text{locus is causal} | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta}) = 1 - p(\mathbf{z} = \mathbf{0} | \boldsymbol{\phi}, \mathbf{x}, \boldsymbol{\theta})$$

BVSLR can be extended to multiple studies

$$\begin{aligned} mL(\boldsymbol{\theta}) &= p(\boldsymbol{\phi} | \mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_S, \boldsymbol{\theta}) \\ &= \int p(\boldsymbol{\phi} | \mathbf{x}_1, \mathbf{x}_2, \dots, \mathbf{x}_S, \mathbf{v}) p(\mathbf{v} | \boldsymbol{\theta}) d\mathbf{v} \rightarrow \max \end{aligned}$$

Assuming the quasi-Laplace approximation holds for each study,

$$\begin{aligned} \prod_{s=1}^S [p(\boldsymbol{\phi} | \mathbf{x}_s, \mathbf{v}) \mathcal{N}(\mathbf{v} | \tilde{\boldsymbol{\mu}}_{\mathbf{z},s}, \text{diag}(\tilde{\boldsymbol{\sigma}}_{\mathbf{z},s}^2))] &\propto \prod_{s=1}^S \mathcal{N}(\mathbf{v} | \tilde{\mathbf{v}}_s, \tilde{\boldsymbol{\Lambda}}_s^{-1}) \\ &= \mathcal{N}(\mathbf{v} | \tilde{\mathbf{v}}, \tilde{\boldsymbol{\Lambda}}^{-1}) \end{aligned}$$

where $\tilde{\boldsymbol{\Lambda}} = \sum_{s=1}^S \tilde{\boldsymbol{\Lambda}}_s$ and $\tilde{\mathbf{v}} = \tilde{\boldsymbol{\Lambda}}^{-1} \sum_{s=1}^S \tilde{\boldsymbol{\Lambda}}_s \tilde{\mathbf{v}}_s$