A General Framework for Variable Selection in Linear Mixed Models with Applications to Genetic Studies with Structured Populations

Joint work with

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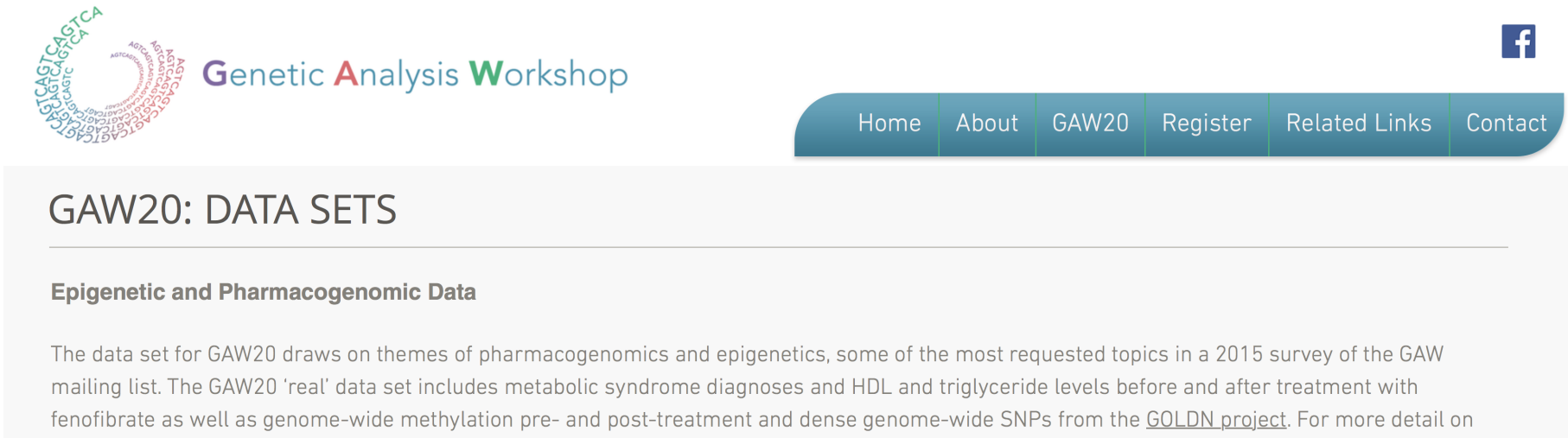
JSM, Vancouver 2018

sahirbhatnagar.com/ggmix

Motivation

Genetic Analysis Workshop (GAW20, March 4-7, 2017, San Diego, US)



[1] GOLDEN project: Genetics of Lipid Lowering Drugs and Diet Network Study

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- Our contribution in GAW20

Investigating potential causal relationships between SNPs, DNA methylation and HDL

Lai Jiang[1,2], Kaiqiong Zhao[1,2], Kathleen Klein[2], Angelo J Canty[5],
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- Contribution of the Causal modelling group

Causal modeling in a multi-omics setting: insights from Genetic Analysis Workshop 20

Jonathan Auerbach*, Richard Howey*, Lai Jiang*, Anne Justice*, Liming Li*, Karim Oualkacha*, Sergi Sayols-Baixeras*, Stella W. Aslibekyan†

*Contributed equally; listed in alphabetical order

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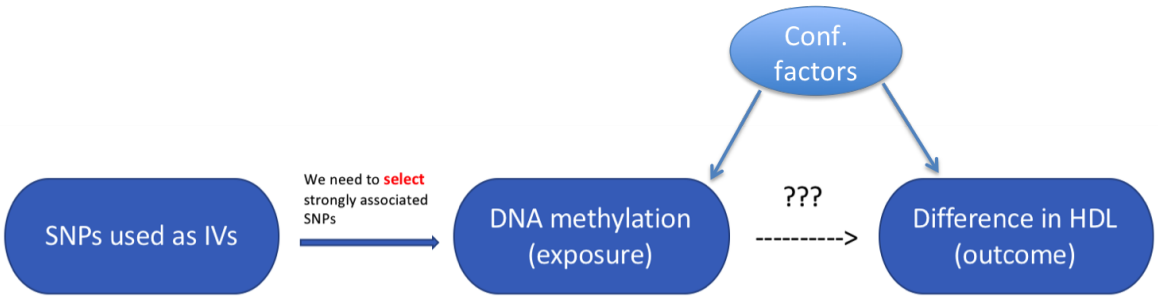

Challenges in GAW20 Data Sets

- GAW20 SNPs data was high-dimensional
- There was a need for data regularization in order to select SNPs strongly associated with the exposure
- Penalized LS regression can be used (Lasso, SCAD, MCP or Elastic net)

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  - either did not control for the family structure
  - or used two-steps adjustment for the family structure (including our group)

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[1] Oualkacha et al. Gene. Epi. (2013)

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Challenges in GAW20 Data Sets

- Two-steps adjustment:
  - Step 1 : uses LMM to adjust for subjects relationship
  - Step 2 : uses residuals from Step 1 in variable-selection LS-regression methods to select SNPs
- Two-steps procedure is a valid approach
- In association testing, (GRAMMAR) it is known to suffer from huge power loss [1]

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Proposal

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We propose, `ggmix`, a two-in-one procedure which controls for structured populations and performs variable selection in Linear Mixed Models

Data and Model

- Phenotype: $\mathbf{Y} = (y_1, \ldots, y_n) \in \mathbb{R}^n$
- SNPs: $\mathbf{X} = (\mathbf{X}_1; \ldots, \mathbf{X}_n)^T \in \mathbb{R}^{n \times p}$, where $p \gg n$
- Twice the Kinship matrix or Realized Relationship matrix: $\mathbf{\Phi} \in \mathbb{R}^{n \times n}$
- Regression Coefficients: $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)^T \in \mathbb{R}^p$
- Polygenic random effect: $\mathbf{P} = (P_1, \ldots, P_n) \in \mathbb{R}^n$
- Error: $\boldsymbol{\varepsilon} = (\varepsilon_1, \ldots, \varepsilon_n) \in \mathbb{R}^n$

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- Error: $\boldsymbol{\varepsilon} = (\varepsilon_1, \ldots, \varepsilon_n) \in \mathbb{R}^n$
- We consider the following LMM with a single random effect:

$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{P} + \boldsymbol{\varepsilon}$$

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

- σ^2 is the phenotype total variance
- $\eta \in [0, 1]$ is the phenotype heritability (narrow sens)
- $\mathbf{Y}|(\boldsymbol{\beta}, \eta, \sigma^2) \sim \mathcal{N}(\mathbf{X}\boldsymbol{\beta}, \eta\sigma^2\mathbf{\Phi} + (1-\eta)\sigma^2\boldsymbol{\mathcal{I}})$

Likelihood

- The negative log-likelihood is given by

$$-\ell(\mathbf{\Theta}) \propto \frac{n}{2}\log(\sigma^2) + \frac{1}{2}\log\left(\det(\mathbf{V})\right) + \frac{1}{2\sigma^2}\left(\mathbf{Y} - \mathbf{X}\beta\right)^T \mathbf{V}^{-1}\left(\mathbf{Y} - \mathbf{X}\beta\right)$$

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- Assume the spectral decomposition of $\boldsymbol{\Phi}$

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with $\mathbf{W} = \text{diag}\left(w_i\right)_{i=1}^n$, $w_i = \eta\mathbf{D}_{ii} + (1-\eta)$

Likelihood

- Projection of $\mathbf{Y}$ (and columns of $\mathbf{X}$) into Span($\mathbf{U}$) leads to a simplified correlation structure for the transformed data: $\tilde{\mathbf{Y}} = \mathbf{U}^\top \mathbf{Y}$
- $\tilde{\mathbf{Y}} | (\beta, \eta, \sigma^2) \sim \mathcal{N}(\tilde{\mathbf{X}}\beta, \sigma^2 \mathbf{W})$, with $\tilde{\mathbf{X}} = \mathbf{U}^\top \mathbf{X}$

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- For fixed σ^2 and η, solving for β is a weighted least squares problem

Penalized Maximum Likelihood Estimator

- Define the objective function:

$$Q_\lambda(\boldsymbol{\Theta}) = -\ell(\boldsymbol{\Theta}) + \lambda \sum_j p_j(\beta_j)$$

- $p_j(\cdot)$ is a penalty term on $\beta_1, \ldots, \beta_p$
- An estimate of the model parameters $\widehat{\boldsymbol{\Theta}}_\lambda$ is obtained by

$$\widehat{\boldsymbol{\Theta}}_\lambda = \arg\min_{\boldsymbol{\Theta}} Q_\lambda(\boldsymbol{\Theta})$$

Block Relaxation (De Leeuw, 1994)

To solve for the optimization problem we use a block relaxation technique

Set $k \leftarrow 0$, initial values for the parameter vector $\boldsymbol{\Theta}^{(0)}$ and ϵ;
for $\lambda \in \{\lambda_{max}, \ldots, \lambda_{min}\}$ **do**
  repeat
    For $j = 1, \ldots, p$,

$$\beta_j^{(k+1)} \leftarrow \arg\min_{\beta_j} Q_\lambda \left(\boldsymbol{\beta}_{-j}^{(k)}, \eta^{(k)}, \sigma^{2\ (k)}\right)$$

$$\eta^{(k+1)} \leftarrow \arg\min_{\eta} Q_\lambda \left(\boldsymbol{\beta}^{(k+1)}, \eta, \sigma^{2\ (k)}\right)$$

$$\sigma^{2\ (k+1)} \leftarrow \arg\min_{\sigma^2} Q_\lambda \left(\boldsymbol{\beta}^{(k+1)}, \eta^{(k+1)}, \sigma^2\right)$$

    $k \leftarrow k + 1$
  until *convergence criterion is satisfied:* $||\boldsymbol{\Theta}^{(k+1)} - \boldsymbol{\Theta}^{(k)}||_2 < \epsilon$;
end

Algorithm 1: Block Relaxation Algorithm

Coordinate Gradient Descent Method

- We take advantage of smoothness of $\ell(\mathbf{\Theta})$
- We approximate $Q_\lambda(\mathbf{\Theta})$ by a strictly convex quadratic function (using gradient)
- We use CGD to calculate a descent direction
- To achieve the descent property for the objective function, we employ further line search

[1] Tseng P& Yun S. Math. Program., Ser. B, (2009)

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Theorem [Convergence] [1]**:**
If $\{\mathbf{\Theta}^{(k)}, k = 0, 1, 2, \ldots\}$ is a sequence of iterates generated by the iteration map of Algorithm 1, then each cluster point (i.e. limit point) of $\{\mathbf{\Theta}^{(k)}, k = 0, 1, 2, \ldots\}$ is a stationary point of $Q_\lambda(\mathbf{\Theta})$

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Choice of the tuning parameter

- We use the BIC:

$$BIC_\lambda = -2\ell(\widehat{\boldsymbol{\beta}}, \widehat{\sigma}^2, \widehat{\eta}) + c \cdot \widehat{df}_\lambda$$

- $\widehat{df}_\lambda$ is the number of non-zero elements in $\widehat{\boldsymbol{\beta}}_\lambda$ plus two [1]
- Several authors [2] have used this criterion for variable selection in mixed models with $c = \log n$
- Other authors [3] have proposed $c = \log(\log(n)) * \log(n)$

[1] Zou et al. The Annals of Statistics, (2007)
[2] Bondell et al. Biometrics (2010)
[3] Wang et al. JRSS(Ser. B), (2009)

Simulation study

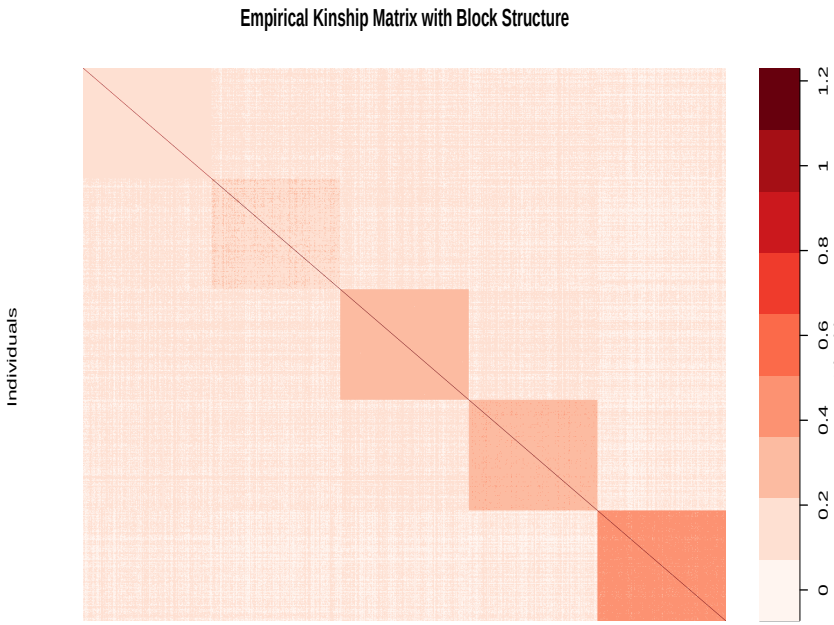
- We simulate genotypes from the BN-PSD Admixture Model
- a : percentage of causal SNPs
- $\mathbf{X}^{(test)}$: $n \times 5000$ matrix of SNPs randomly sampled across the genome
- $\mathbf{X}^{(causal)}$: $n \times (a * 5000)$ matrix of SNPs that are truly associated with the simulated phenotype, $\mathbf{X}^{(causal)} \subseteq \mathbf{X}^{(test)}$
- β_j: effect size for the j^{th} SNP, simulated from a $Uniform(0.3, 0.7)$ for $j = 1, \ldots, (a * 5000)$
- $\mathbf{Y}|(\boldsymbol{\beta}, \eta, \sigma^2) \sim \mathcal{N}(\mathbf{X}^{(causal)}\boldsymbol{\beta}, \eta\sigma^2\boldsymbol{\Phi} + (1-\eta)\sigma^2\boldsymbol{\mathcal{I}})$

[1] `https://cran.r-project.org/package=bnpsd`

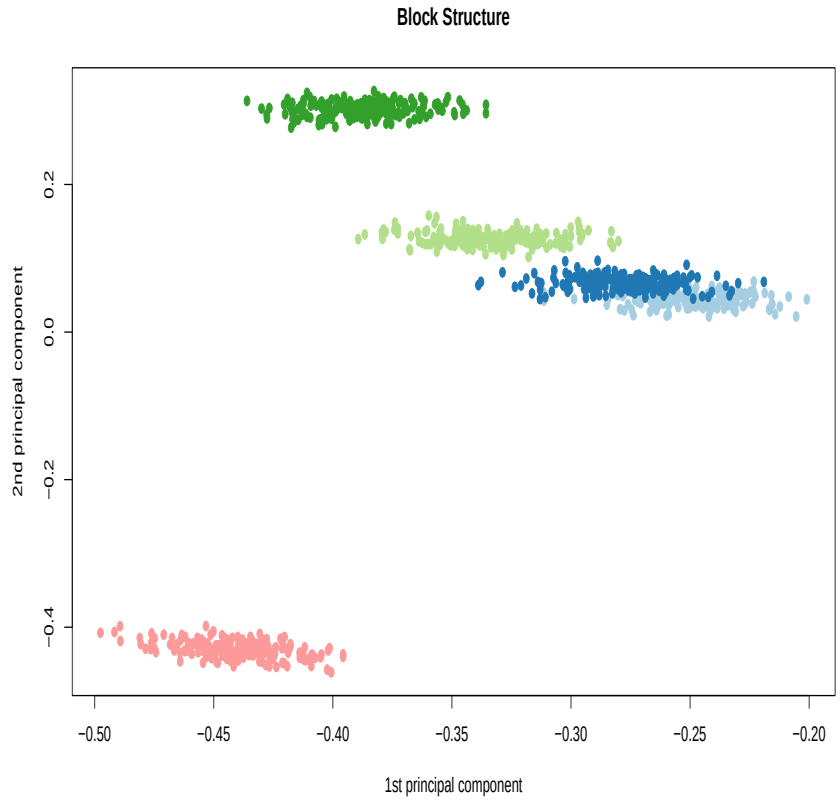
RRM/Kinship matrix construction

- $\mathbf{X}^{(other)}$: $n \times 10,000$ matrix of simulated SNPs
- $\mathbf{X}^{(kinship)}$: matrix of SNPs used to construct the RRM/Kinship matrix
  - Scenario 1: $\mathbf{X}^{(kinship)} = \mathbf{X}^{(other)} \leftarrow$ No overlap
  - Scenario 2: $\mathbf{X}^{(kinship)} = [\mathbf{X}^{(other)}, \mathbf{X}^{(causal)}] \leftarrow$ 100% overlap
- In each scenario we considered $a = 0, 0.01$, $\eta = 0.1, 0.5$ and $\sigma^2 = 1$

Empirical Kinship Matrix

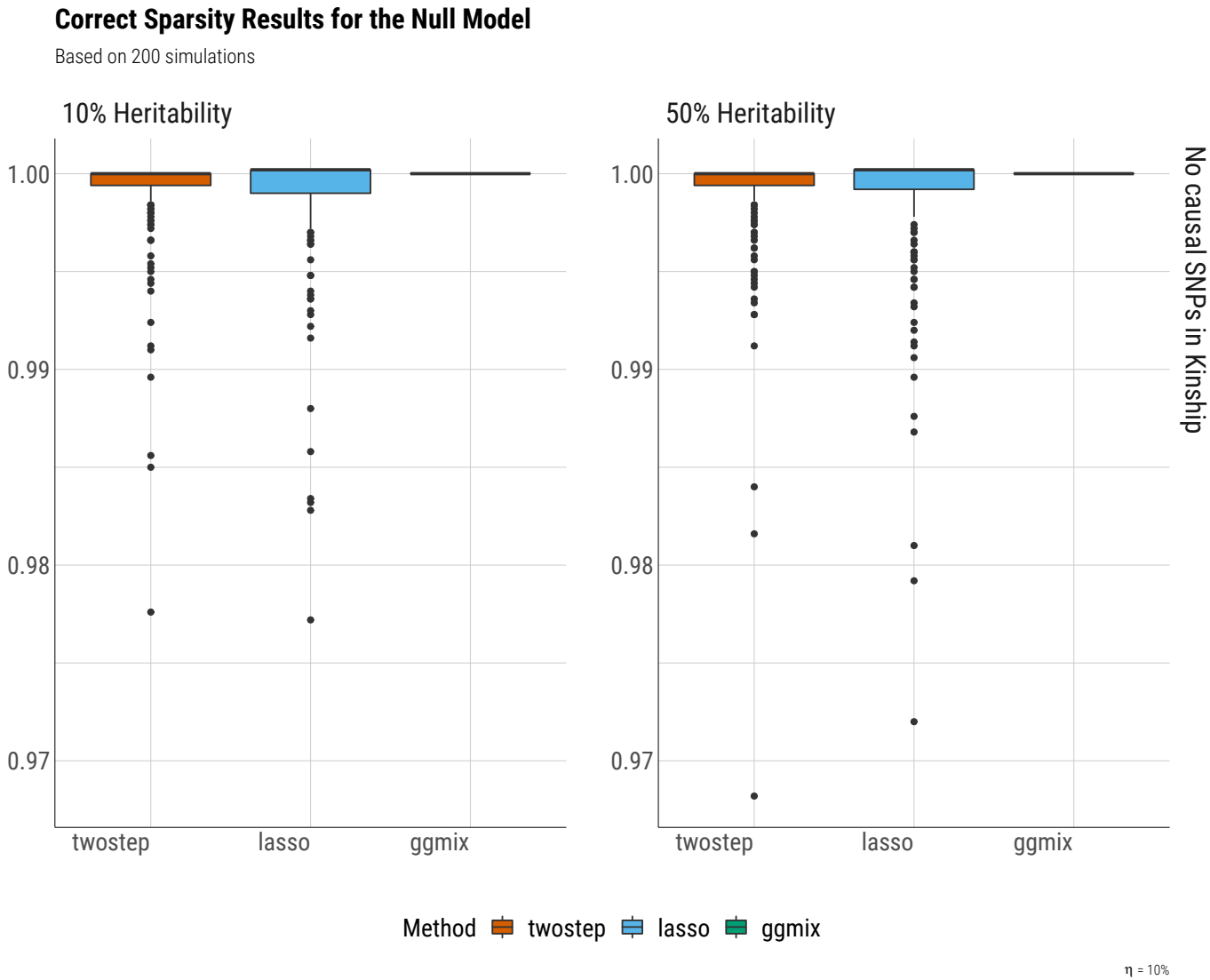


(a) Kinship Matrix

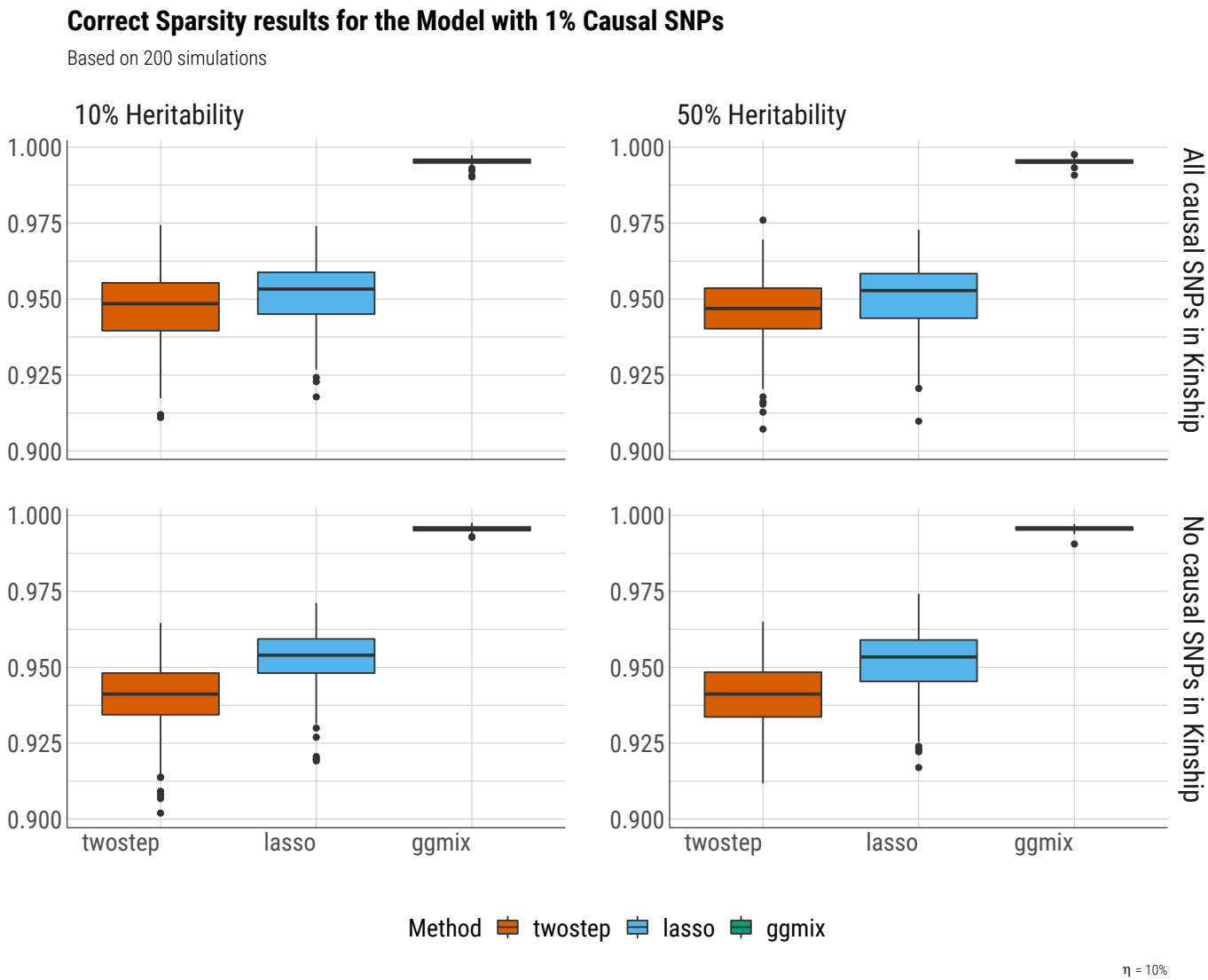


(b) 1st and 2nd PC

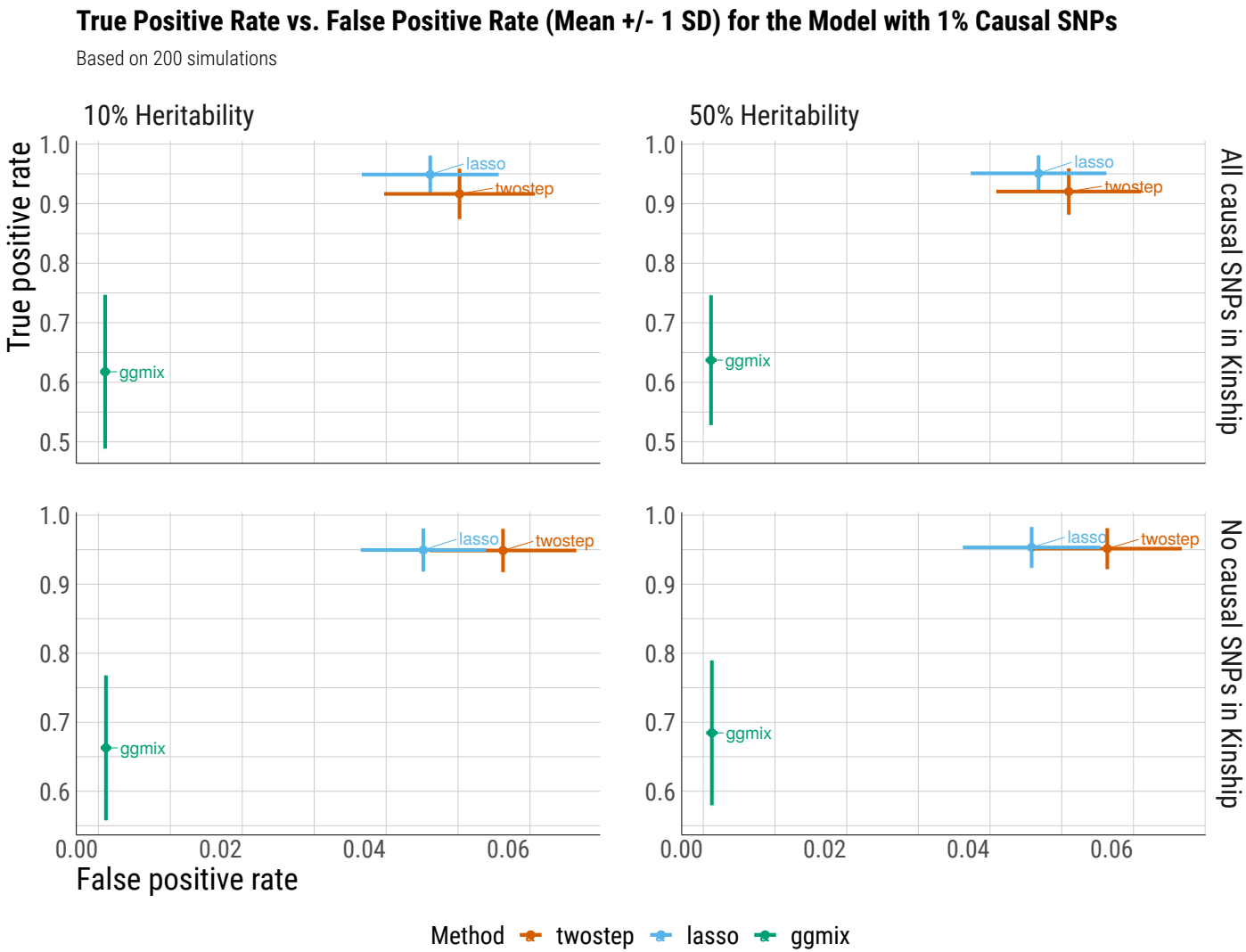
Correct Sparsity for Null Model



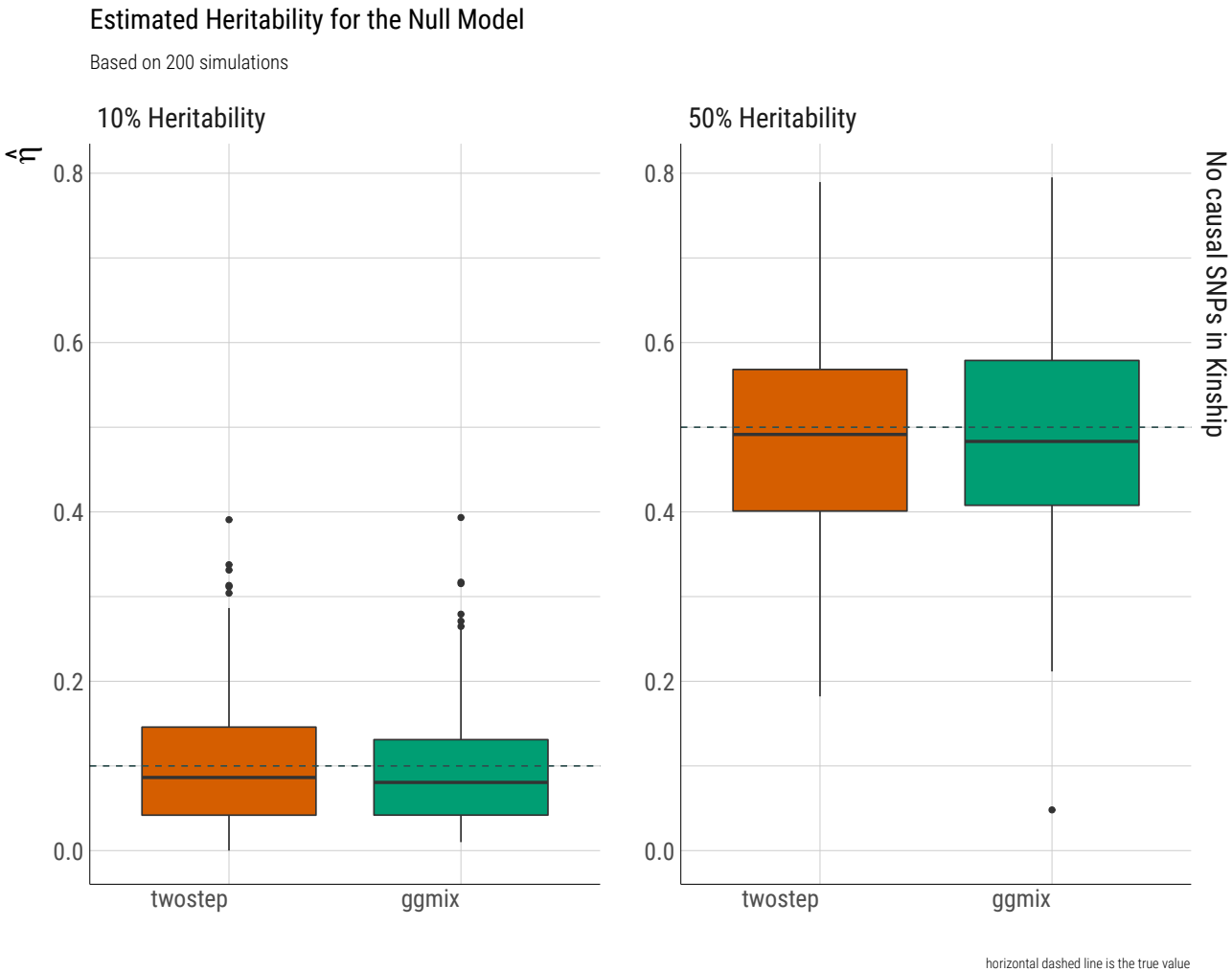
Correct Sparsity for Model with 1% Causal SNPs



True Positive vs. False Positive Rate



Heritability Estimates for Null Model



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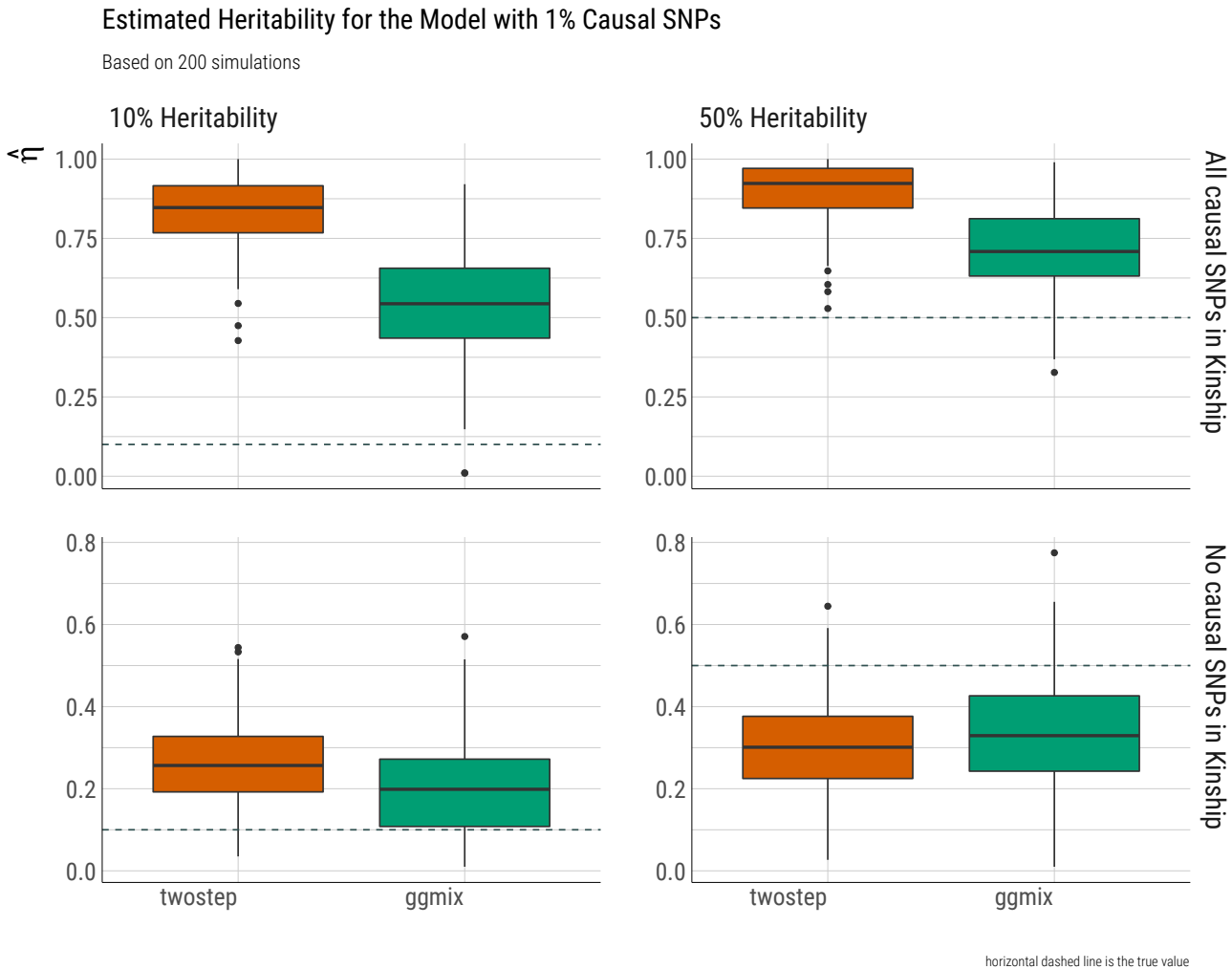
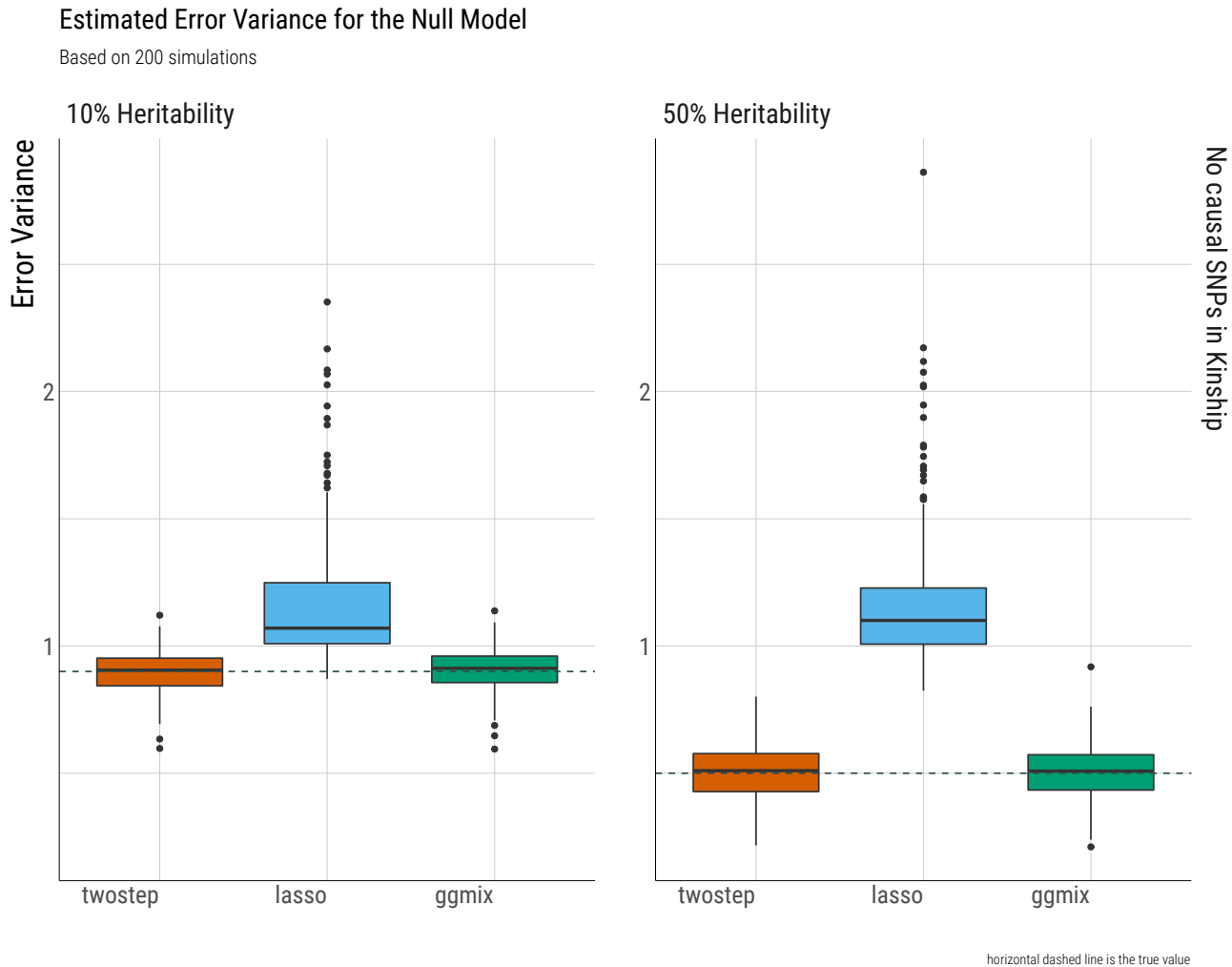
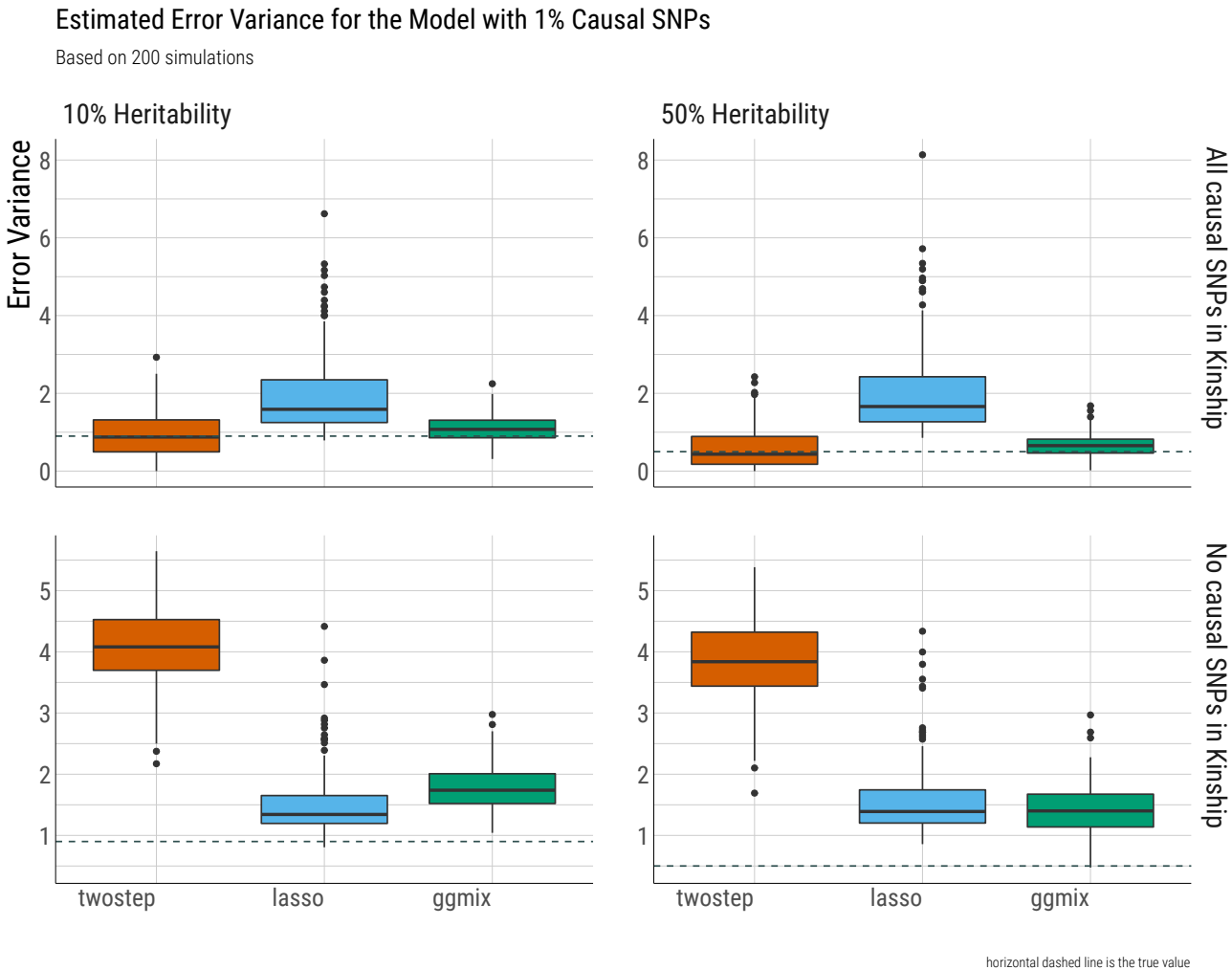


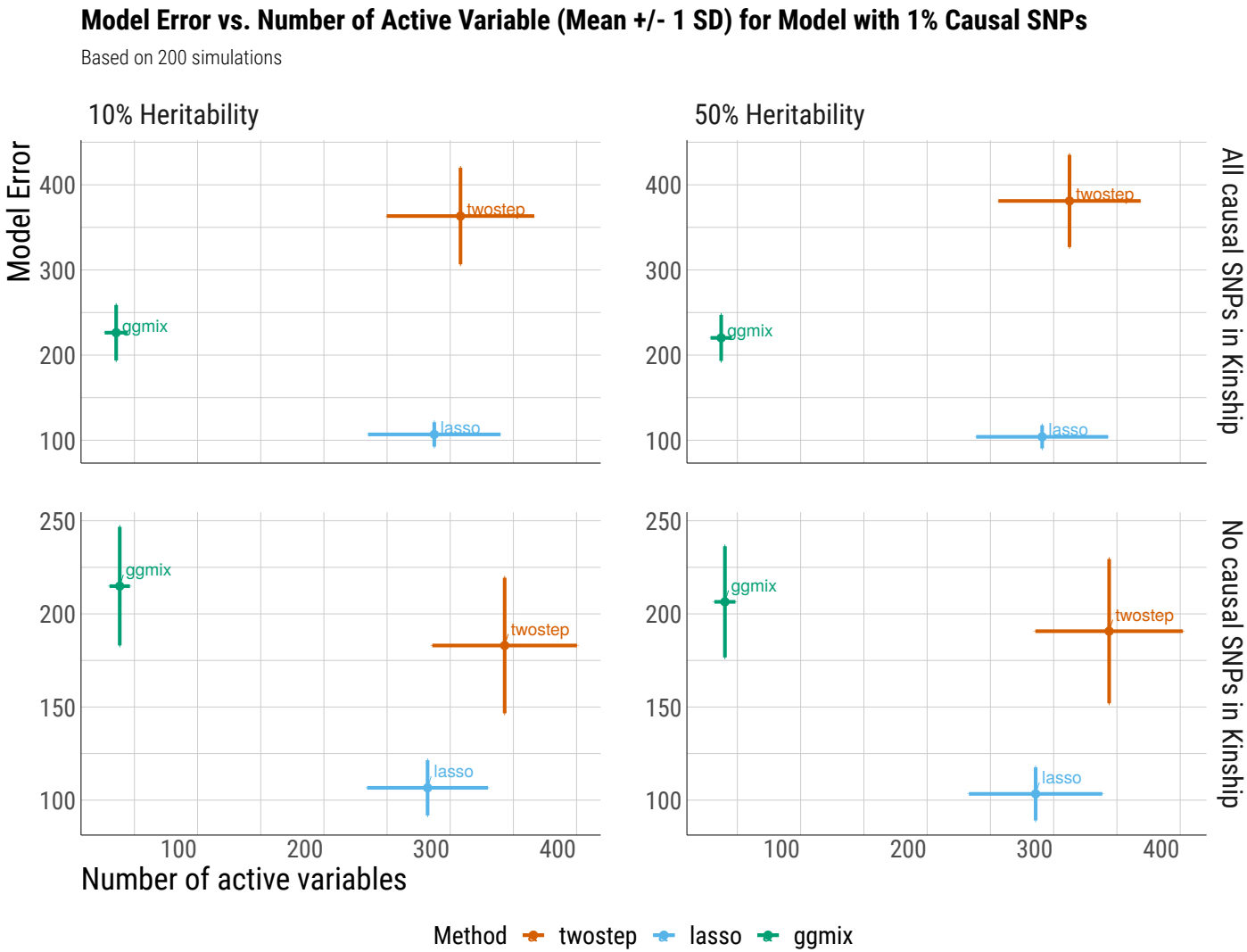
Error Variance for Null Model



Error Variance for Model with 1% Causal SNPs



Model Error vs. Number Active for Model with 1% Causal SNPs



Discussion/Future work

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- Theoretical development of group-Lasso in LMM is already done
- In situations where the RRM matrix is of low rank (i.e. $n >> \#$ of SNPs used to construct RRM). ex: UK Biobank
- Computational time of fitting `ggmix` can be reduced using SVD decomposition of $\mathbf{X}^{(kinship)}$ in order to construct $\mathbf{\Phi}$ and in order to transforme the data
- Theoretical development of low-rank trick is already done

Discussion/Future work

- Capturing the subjects relationship using random effect requires VCs estimation
- Random effect modelling leads to a non-convex optimization problem
- Fixed effects models are good alternatives to random effects models for analysis of Longitudinal/Panel data [1]
- Capturing familial structure using a penalized FE model could be an interesting avenue to explore

[1] Roger Koenker, JMA, (2004)

References

1. Christoph Lippert, Jennifer Listgarten, Ying Liu, Carl M Kadie, Robert I Davidson, and David Heckerman. Fast linear mixed models for genome-wide association studies. Nature methods, 8(10):833–835, 2011.
2. Matti Pirinen, Peter Donnelly, Chris CA Spencer, et al. Efficient computation with a linear mixed model on large-scale data sets with applications to genetic studies. The Annals of Applied Statistics, 7(1):369–390, 2013.
3. Paul Tseng and Sangwoon Yun. A coordinate gradient descent method for nonsmooth separable minimization. Mathematical Programming, 117(1):387–423, 2009.
4. Jerome Friedman, Trevor Hastie, and Rob Tibshirani. Regularization paths for gen- eralized linear models via coordinate descent. Journal of statistical software, 33(1):1, 2010.

`sahirbhatnagar.com/ggmix`