Parallelized Markov chain Monte Carlo algorithms utilizing GPUs with an application to RNAseq data analysis

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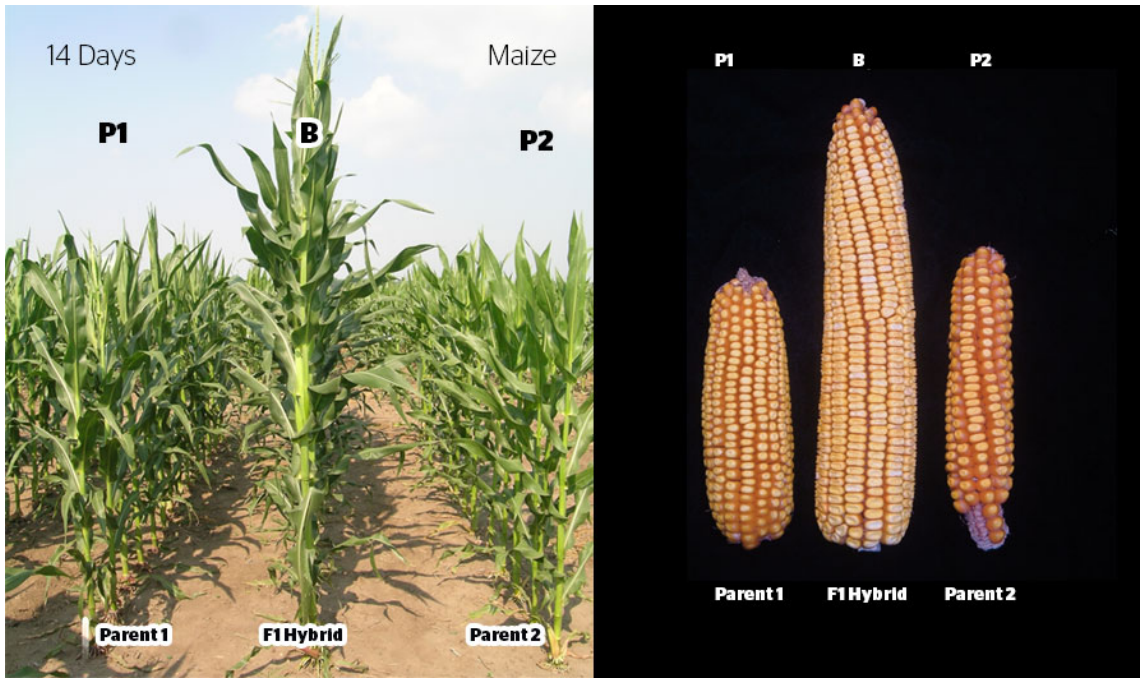
Heterosis

Definition

Heterosis, or hybrid vigor, is the enhancement of the phenotype of hybrid progeny relative to their inbred parents.



(`http://www2.iastate.edu/~nscentral/news/06/may/vigor.shtml` modified by Will Landau)

RNAseq data

Gene ID	B73				Mo17				B73 x Mo17				Mo17 x B73			
GRMZM2G107839	26	17	32	35	30	32	41	43	63	44	116	101	30	31	69	47
GRMZM5G899787	62	57	38	33	91	78	66	69	58	84	42	43	74	70	53	51
GRMZM5G899800	150	238	12	6	198	392	11	15	187	433	8	10	414	291	11	13
GRMZM2G301485	24	12	29	32	20	14	32	46	5	3	6	6	2	3	3	7
GRMZM5G899836	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...

(Will Landau)

- Low parent heterosis (LPH): expression in hybrid is lower than both parents
- High parent heterosis (HPH): expression in hybrid is higher than both parents

Posterior hypothesis probabilities

If we had a posterior distribution for the mean expression levels, i.e.

$$p(\mu_B, \mu_M, \mu_{BM}, \mu_{MB}|y)$$

where y represents our data, then we could calculate the relevant hypothesis probabilities, i.e.

$$\begin{aligned} P(H_0 \quad |y) &= P(\mu_{min} < \mu_{BM} < \mu_{max}|y) \\ P(H_{LPH}|y) &= P(\mu_{BM} < \mu_{min}|y) \\ P(H_{HPH}|y) &= P(\mu_{max} < \mu_{BM}|y) \end{aligned}$$

where $\mu_{min} = \min(\mu_B, \mu_M)$ and $\mu_{max} = \max(\mu_B, \mu_M)$.

Hierarchical modeling *partially pools* the information across genes and thereby provides a data-based multiple comparison adjustment by

- shrinking estimates toward a grand mean (or zero) based on the variability inherent in the data and
- reducing posterior uncertainty by borrowing information across genes.

(Gelman, Hill, and Yajima (2012))

Overdispersed count regression model

Let

- g $(g = 1, \ldots, G)$ identify the gene,
- n $(n = 1, \ldots, N)$ identify the sample,
- y be the $G \times N$ matrix of RNAseq counts and
- X be the $N \times L$ model matrix that connects the N samples to the varieties, blocking factors, etc.

We assume

$$y_{gn} \overset{ind}{\sim} \text{Po}\left(e^{h_n + \varepsilon_{gn} + x_n' \beta_g}\right)$$

where

- h_n are *normalization factors*,
- $\varepsilon_{gn} \overset{ind}{\sim} N(0, \gamma_g)$ allow for gene-specific overdispersion,
- x_n is the n^{th} row of X, and
- β_g is a vector of length L that account for effects on gene expression of variables of interest.

Hierarchical model

Recall

$$y_{gn} \overset{ind}{\sim} \text{Po}\left(e^{h_n+\varepsilon_{gn}+x_n'\beta_g}\right) \qquad \text{and} \qquad \varepsilon_{gn} \overset{ind}{\sim} N(0, \gamma_g).$$

We construct a hierarchical model for both γ_g and β_g to borrow information across genes. Specifically, we assume

$$1/\gamma_g \overset{ind}{\sim} \text{Ga}\left(\nu/2, \nu\tau/2\right)$$

such that $E[1/\gamma_g] = 1/\tau$ and $CoV[1/\gamma_g] = \sqrt{2/\nu}$ and

$$\beta_{g\ell} \overset{ind}{\sim} N(\theta_\ell, \sigma_\ell^2)$$

for $\ell = 1, \ldots, L$.

Model matrix for our heterosis experiment

Experimental design: 4 varieties, 2 plates, 2 replicates per variety per plate

$$X = \left(\begin{bmatrix} 1 & 1 & -1 & 0 \\ 1 & -1 & 1 & 0 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & -1 \end{bmatrix} \otimes J_{(N/4)\times 1} \qquad J_{(N/4)\times 1} \otimes \begin{bmatrix} 1 \\ 1 \\ -1 \\ -1 \end{bmatrix} \right)$$

where $\otimes$ denotes the Kronecker product and $J_{m\times n}$ is the m by n matrix with all entries equal to 1.

Interpretations of the gene-specific parameters (dropping the g subscript) are

- β_1 is the parental mean
- β_2 is the half difference of hybrid mean vs M
- β_3 is the half difference of hybrid mean vs B
- β_4 is the half difference between hybrids
- β_5 is the flow cell block effect

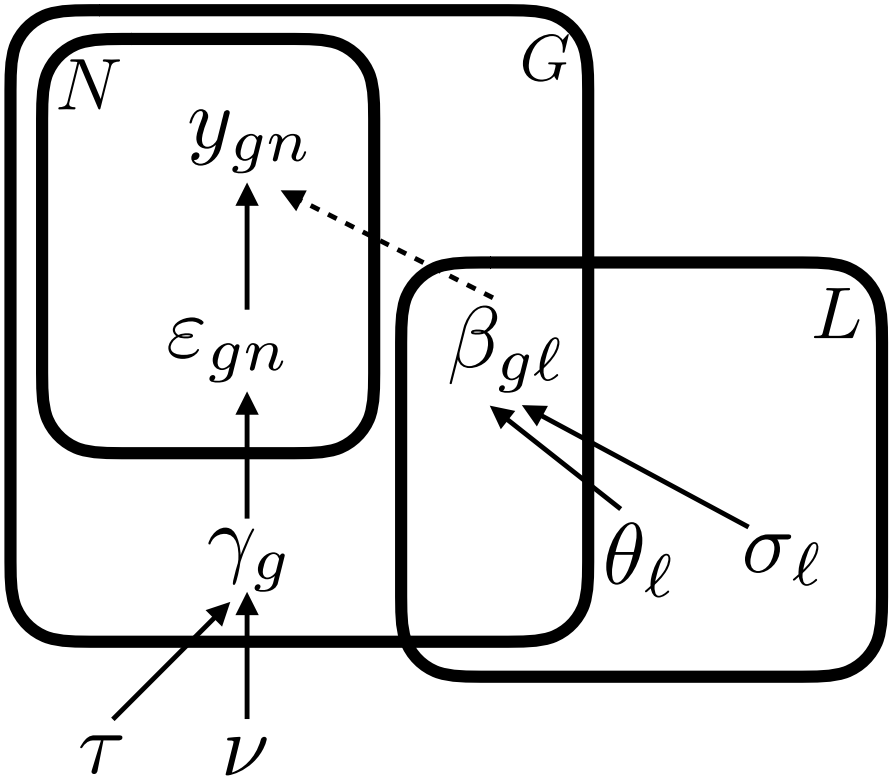
Heterosis hypotheses

Heterosis	With log-scale group means	With $\beta_{g\ell}$ parameters
high-parent BM	$\mu_{g,\text{BM}} > \max\left(\mu_{g,\text{B}}, \mu_{g,\text{M}}\right)$	$2\beta_{g2} + \beta_{g4},\quad 2\beta_{g3} + \beta_{g4} > 0$
low-parent BM	$\mu_{g,\text{BM}} < \min\left(\mu_{g,\text{B}}, \mu_{g,\text{M}}\right)$	$-2\beta_{g2} - \beta_{g4}, -2\beta_{g3} - \beta_{g4} > 0$
high-parent MB	$\mu_{g,\text{MB}} > \max\left(\mu_{g,\text{B}}, \mu_{g,\text{M}}\right)$	$2\beta_{g2} - \beta_{g4},\quad 2\beta_{g3} - \beta_{g4} > 0$
low-parent MB	$\mu_{g,\text{MB}} < \min\left(\mu_{g,\text{B}}, \mu_{g,\text{M}}\right)$	$-2\beta_{g2} + \beta_{g4},\quad 2\beta_{g3} + \beta_{g4} > 0$
high-parent mean	$\mu_{g,\text{BM}} + \mu_{g,\text{MB}} > 2\max\left(\mu_{g,\text{B}}, \mu_{g,\text{M}}\right)$	$\beta_{g2},\quad \beta_{g3} > 0$
low-parent mean	$\mu_{g,\text{BM}} + \mu_{g,\text{MB}} < 2\min\left(\mu_{g,\text{B}}, \mu_{g,\text{M}}\right)$	$-\beta_{g2}, -\beta_{g3} > 0$

All hypothesis regions are intersections of linear combination events, but we can also accomodate unions of contrast events via

$$P(A \cup B) = P(A) + P(B) - P(A \cap B).$$

Directed acyclic graphical model



$$p(\varepsilon, \beta, \gamma, \theta, \sigma, \tau, \nu | y) =$$

$$p(\varepsilon, \beta, \gamma | \tau, \nu, \theta, \sigma, y) \times p(\tau, \nu, \theta, \sigma | y) \propto$$

$$\prod_{g=1}^{G} \left\{ \left[\prod_{n=1}^{N} p(y_{gn} | \beta_g, \varepsilon_{gn}) p(\varepsilon_{gn} | \gamma_g) \right] \left[\prod_{\ell=1}^{L} p(\beta_{g\ell} | \theta_\ell, \sigma_\ell) p(\theta_\ell) p(\sigma_\ell) \right] p(\gamma_g | \tau, \nu) \right\} p(\tau) p(\nu)$$

(Will Landau)

where $G \approx 40\,000$, $N = 16$, and $L = 5$ in our application and thus we have

- $G \times N + G + 2 + G \times L + 2 \times L \approx 800\,000$ parameters
- and $G \times N \approx 640\,000$ observations.

Priors

All priors are constructed to be vague, proper, and (if possible) conditionally conjugate. There are $2(L+1)$ hyperparameters and we assign the following priors

$$\begin{aligned}
\tau &\sim Ga(a, b) && \text{conditionally conjugate} \\
\nu &\sim Unif(0, d) && \\
\theta_\ell &\overset{ind}{\sim} N(0, c_\ell^2) && \text{conditionally conjugate} \\
\sigma_\ell &\overset{ind}{\sim} Unif(0, s_\ell) && \text{(Gelman (2006))}
\end{aligned}$$

As we'll see, posterior distributions for these parameters are extremely tight relative to their priors.

Constructing a Gibbs sampler

Conditional independence within a step:

$$
\begin{aligned}
p(\varepsilon|\ldots) &\propto \prod_{g=1}^{G}\prod_{n=1}^{N} Po\left(y_{gn}\middle|e^{h_n+\varepsilon_{gn}+x_n'\beta_g}\right) N(\varepsilon_{gn}|0,\gamma_g)\\
p(\gamma|\ldots) &\propto \prod_{g=1}^{G}\prod_{n=1}^{N} N\left(\varepsilon_{gn}|0,\gamma_g\right) IG(\gamma_g|\nu/2,\nu\tau/2)\\
p(\beta_\ell|\ldots) &\propto \prod_{g=1}^{G}\prod_{n=1}^{N} Po\left(y_{gn}\middle|e^{h_n+\varepsilon_{gn}+x_n'\beta_g}\right) N(\beta_{g\ell}|\theta_\ell,\sigma_\ell^2)
\end{aligned}
$$

Sufficient "statistics":

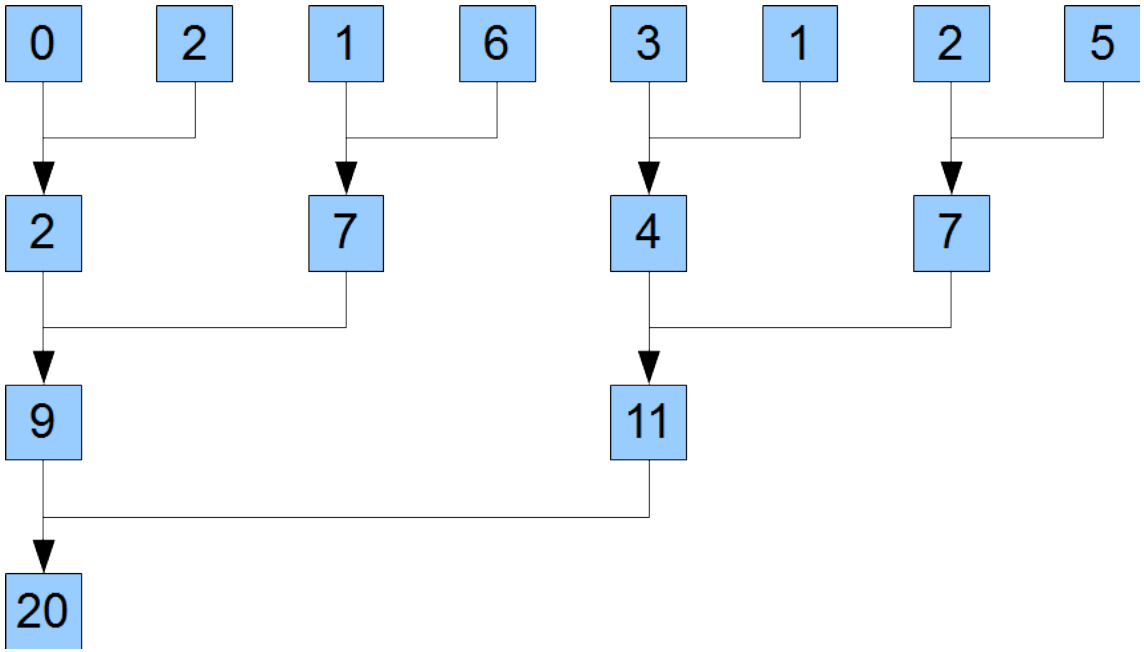
$$
\begin{aligned}
p(\tau|\ldots) &\sim Ga(\tau|a',b') & (a',b') &= f_\tau(\gamma,\nu,a,b)\\
p(\nu|\ldots) &\sim p(\nu|d')\mathrm{I}(0<\nu<d) & d' &= f_\nu(\gamma,\tau,d)\\
p(\theta_\ell|\ldots) &\sim N(\theta_\ell|m_\ell',C_\ell') & (m_\ell',C_\ell') &= f_{\theta_\ell}(\beta_\ell,\sigma_\ell,c_\ell^2)\\
p(\sigma_\ell^2|\ldots) &\sim IG(e',f')\mathrm{I}(0<\sigma_\ell^2<s_\ell^2) & (e',f') &= f_{\sigma_\ell}(\beta_\ell,\theta_\ell)
\end{aligned}
$$

where the functions calculate means, variances, products, etc. over G terms.

Parallelization translated to a GPU

If there are G nodes, then

- Conditional independence $\rightarrow$ embarrassingly parallel - possible speedup is G
- Calculate sufficient "statistics" $\rightarrow$ reduction - possible speedup is $[G-1]/\log_2(G)$



(https://scs.senecac.on.ca/~gpu610/pages/images/parallel_reduction.png)

GPU computing algorithm constraints

Constraint	Solution
memory coalescence	set up proper data structures
only uniform and normal RNGs	step out slice sampler
data transfer speed	thinning
	return draws for a small subset of parameters hyperparameters random set of gene-specific parameters
	calculate running sums for convergence diagnostics normal-based credible intervals hypothesis probabilities

Convergence diagnostics

For each parameter θ over the M iterations of chain c, calculate

$$M\overline{\theta}_c = \sum_{m=1}^{M} \theta_c^{(m)} \qquad \text{and} \qquad M\overline{\theta^2}_c = \sum_{m=1}^{M} \left(\theta_c^{(m)}\right)^2.$$

using a numerically stable one-pass (or online) algorithm.

Compute the Gelman-Rubin convergence diagnostic amongst C chains using

$$\widehat{R} = \sqrt{1 + \frac{1}{M}\left(\frac{B}{W} - 1\right)}$$

where

$$B = \frac{M}{C-1}\sum_{c=1}^{C}\left(\overline{\theta}_c - \overline{\theta}\right)^2, W = \frac{1}{C}\sum_{c=1}^{C} S_c^2,$$

$$\overline{\theta} = \frac{1}{C}\sum_{c=1}^{C}\overline{\theta}_c, \text{ and } S_c^2 = \frac{M}{M-1}\left[\overline{\theta^2}_c - \overline{\theta}_c^2\right] \approx \overline{\theta^2}_c - \overline{\theta}_c^2.$$

Normal-based credible intervals

For the collection of parameters ψ and under regularity conditions, we have

$$p_N(\psi|y_N) \xrightarrow{d} N\left(\psi_0, [\mathrm{I}_N(\psi_0)]^{-1}\right)$$

as $N \to \infty$ where ψ_0 is the true value and $\mathrm{I}_N(\psi_0)$ is the Fisher information.

For any scalar parameter θ, we have

$$\theta|y \dot{\sim} N\left(\overline{\theta}, \overline{\theta^2} - \overline{\theta}^2\right)$$

and can construct normal-based credible intervals with

$$\overline{\theta} \pm z_{\alpha/2}\sqrt{\overline{\theta^2} - \overline{\theta}^2}$$

where $P(Z > z_\alpha) = \alpha$ and Z is a standard normal distribution.

Estimating hypothesis probabilities

Recall we are interested in estimating probabilities similar to

$$P(\text{high parent heterosis for the B73}\times\text{Mo17 hybrid}|y)$$

$$= P\left(2\beta_{g2} + \beta_{g4} > 0 \text{ and } 2\beta_{g3} + \beta_{g4} > 0 \middle| y\right)$$

$$\approx \frac{1}{M}\sum_{m=1}^{M} \mathrm{I}\left(2\beta_{g2}^{(m)} + \beta_{g4}^{(m)} > 0\right) \mathrm{I}\left(2\beta_{g3}^{(m)} + \beta_{g4}^{(m)} > 0\right)$$

We can use the running sums to keep track of this sum.

Implementation

The computation for this hierarchical overdispersed count regression model is provided in the following three R packages at `https://github.com/wlandau/`:

- `fbseq`: user interface
- `fbseqOpenMP`: multithreaded backend
- `fbseqCUDA`: NVIDIA GPU backend

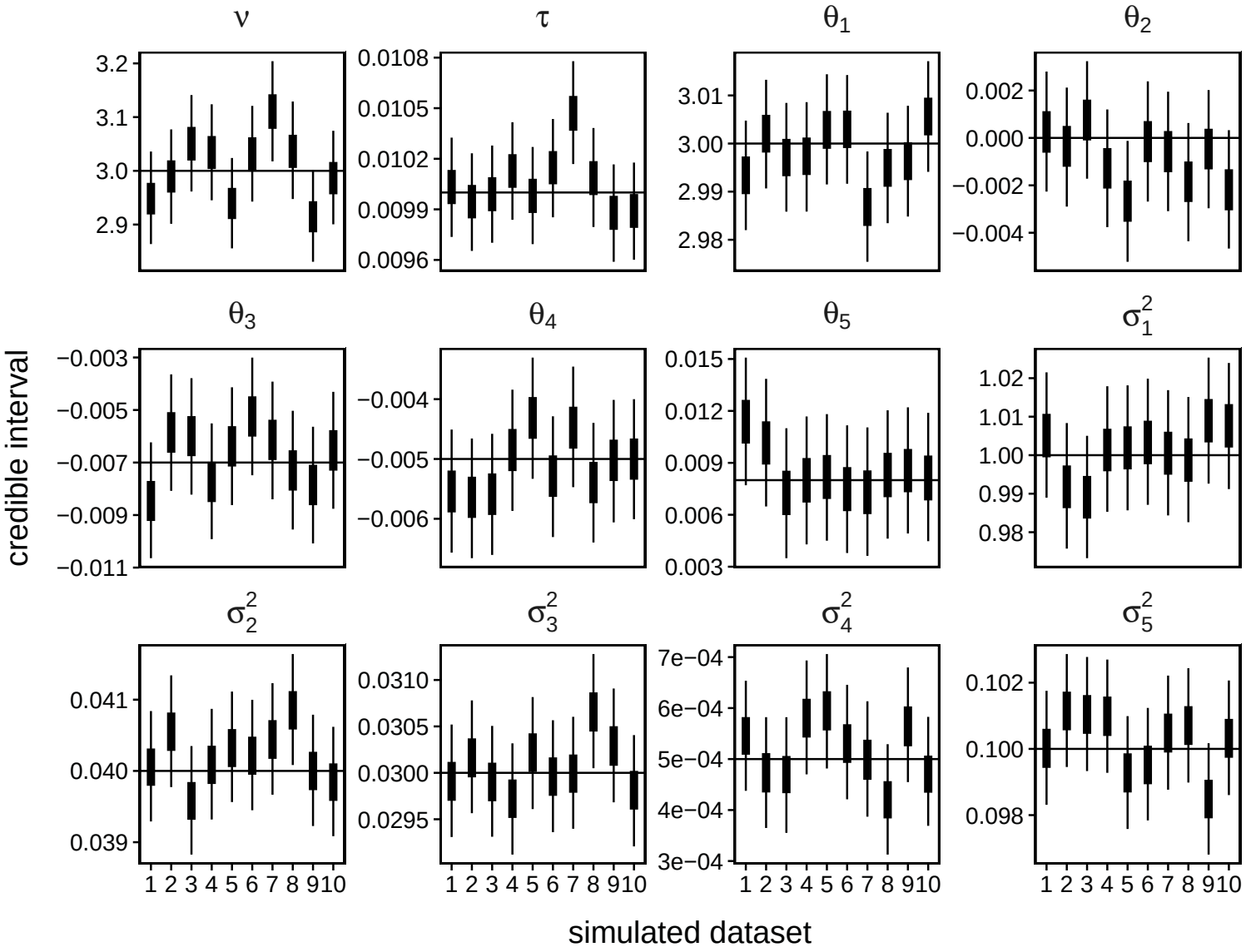
```
library(fbseq)
data(paschold) # Paschold et. al. (2012) data

paschold@contrasts[[5]]


## beta_1 beta_2 beta_3 beta_4 beta_5
##      0      2      0      1      0


paschold@contrasts[[6]]


## beta_1 beta_2 beta_3 beta_4 beta_5
##      0      0      2      1      0


paschold@propositions$`high-parent_B73xMo17`


## high-parent_B73xMo17_1 high-parent_B73xMo17_2
##                      5                      6
```

```
configs    = Configs(burnin = 10, iterations = 10, thin = 1)
chain      = Chain(paschold, configs)
chain_list = fbseq(chain, backend = "CUDA")
```

Simulation studies

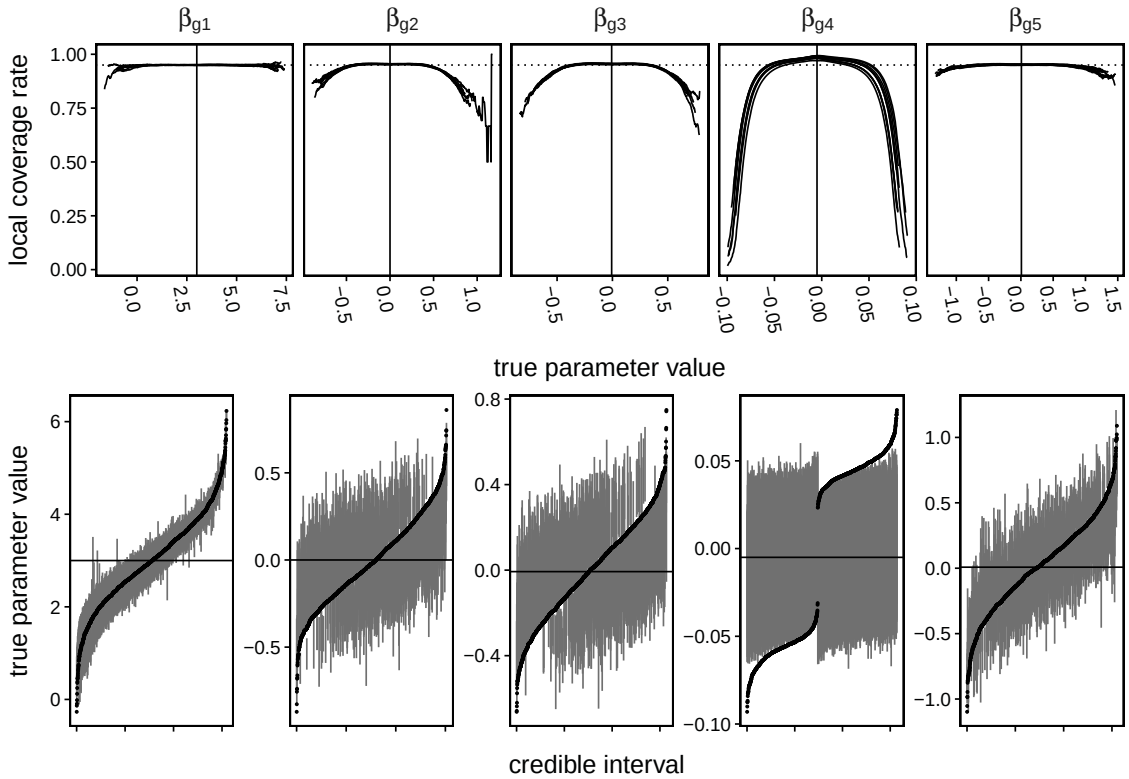
- Simulation model
  - Model: hierarchical count regression model with data-based hyperparameters
  - Simple: count regression model with sparsity in gene-specific parameters
  - edgeR: negative binomial model with data-based gene-specific parameters
- Inference
  - edgeR: non-hierarchical except for overdispersion, negative binomial model
  - fully Bayes: Bayesian analysis with hierarchical count regression model
  - eBayes (Means): empirical Bayesian analysis with hierarchical count regression model with hyperparameter estimated from posterior means of the fully Bayes approach
  - eBayes (Oracle): empirical Bayesian analysis with hierarchical count regression model with true values for the hyperparameters
- Data size
  - $G = 30\,000$
  - $N = 16$ and $N = 32$

Hyperparameter coverage



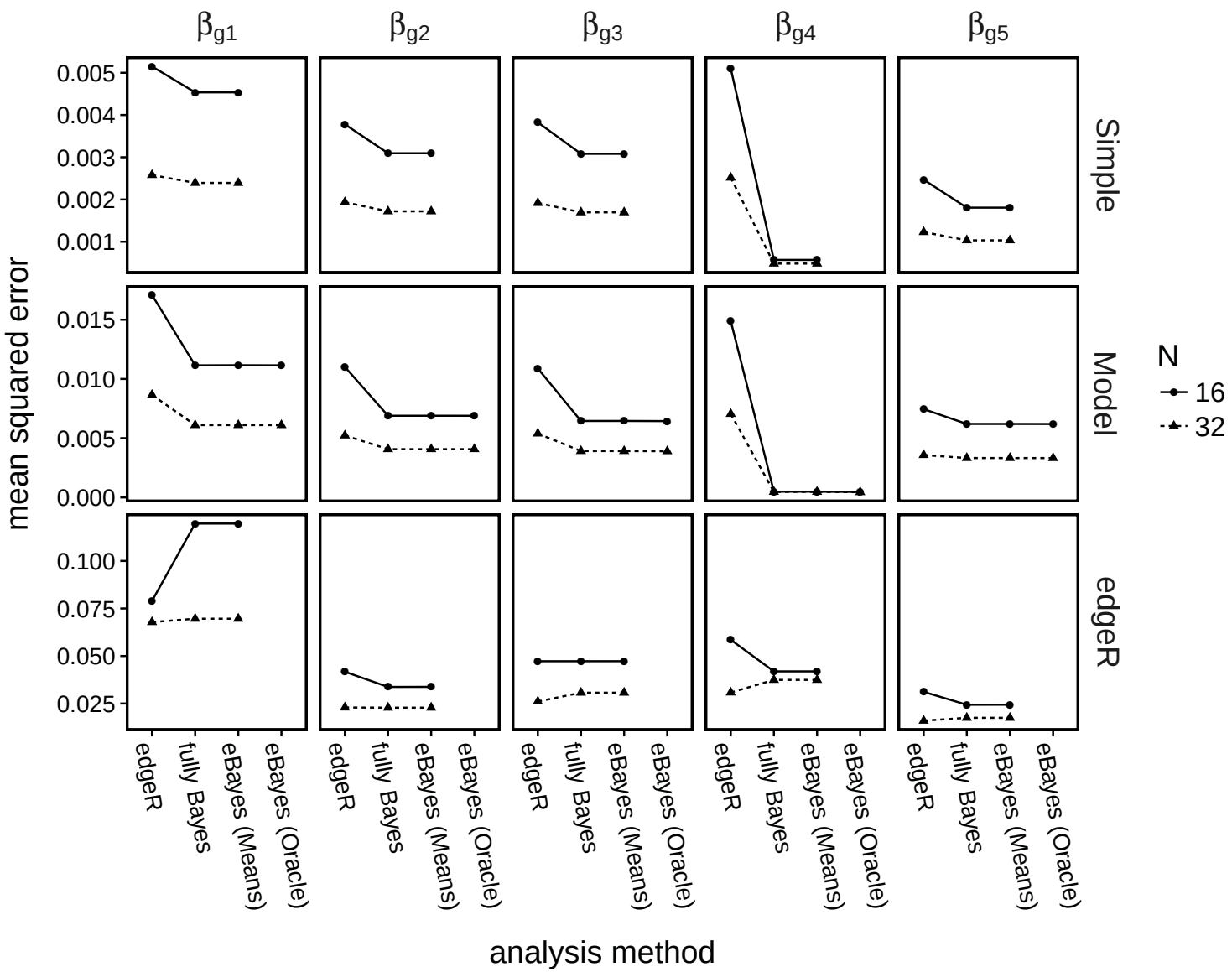
Gene-specific parameter coverage

Overall, we had approximately 95% coverage of 95% credible intervals, but

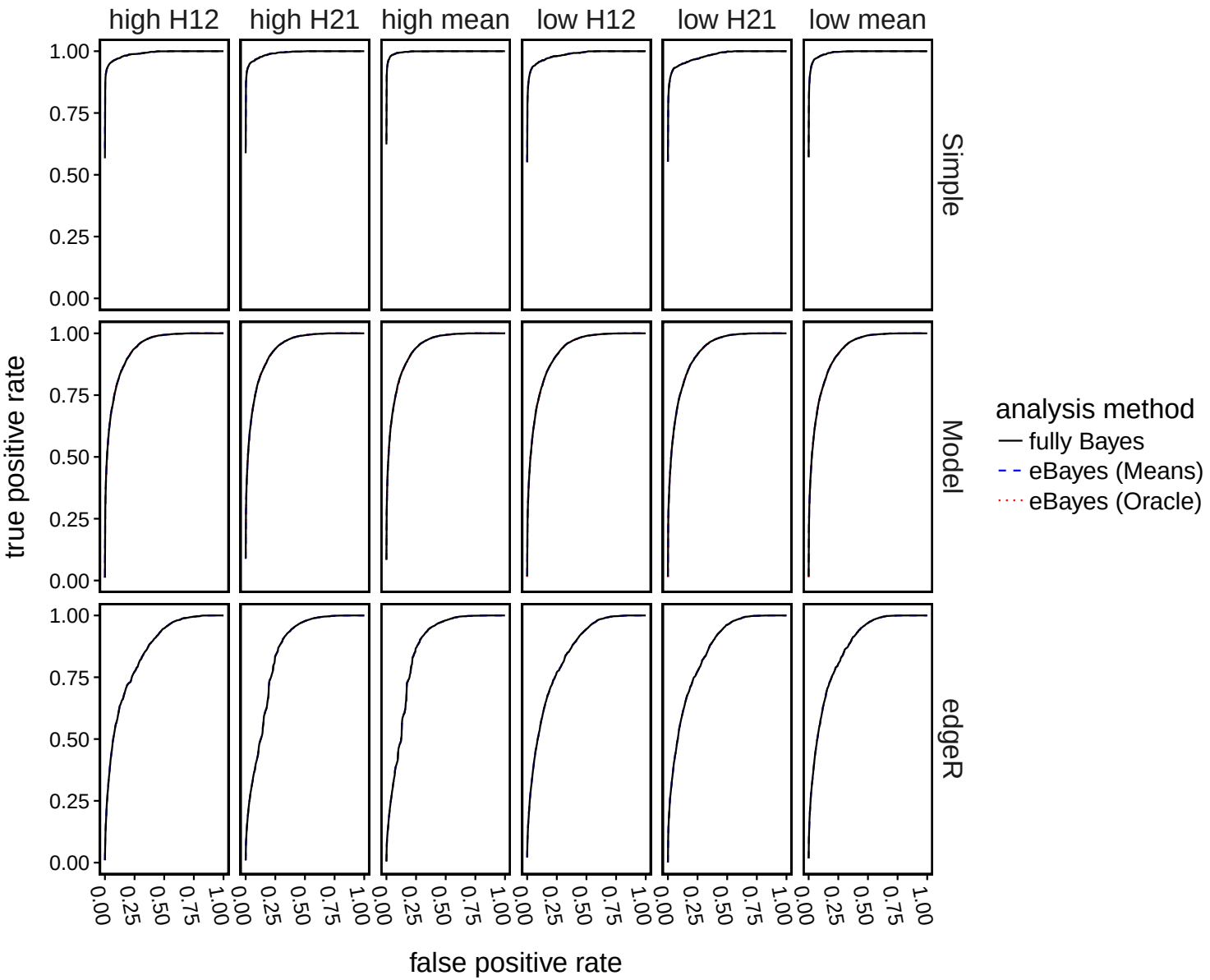


where the lower plot indicates that when the intervals miss, we are overshrinking.

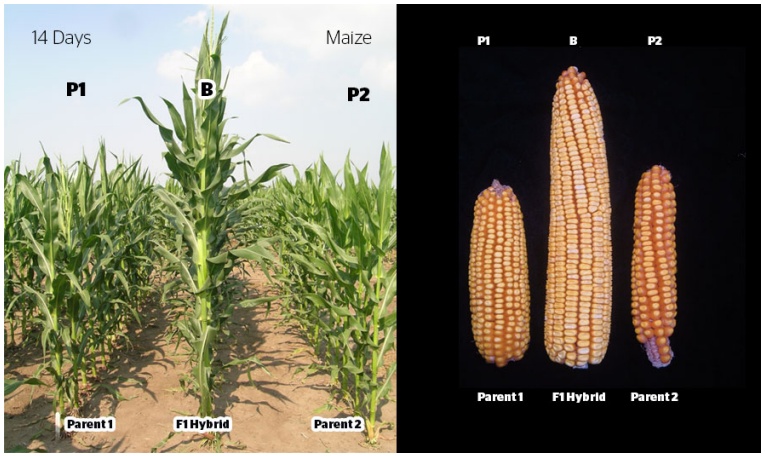
Mean squared error



ROC curves for heterosis detection

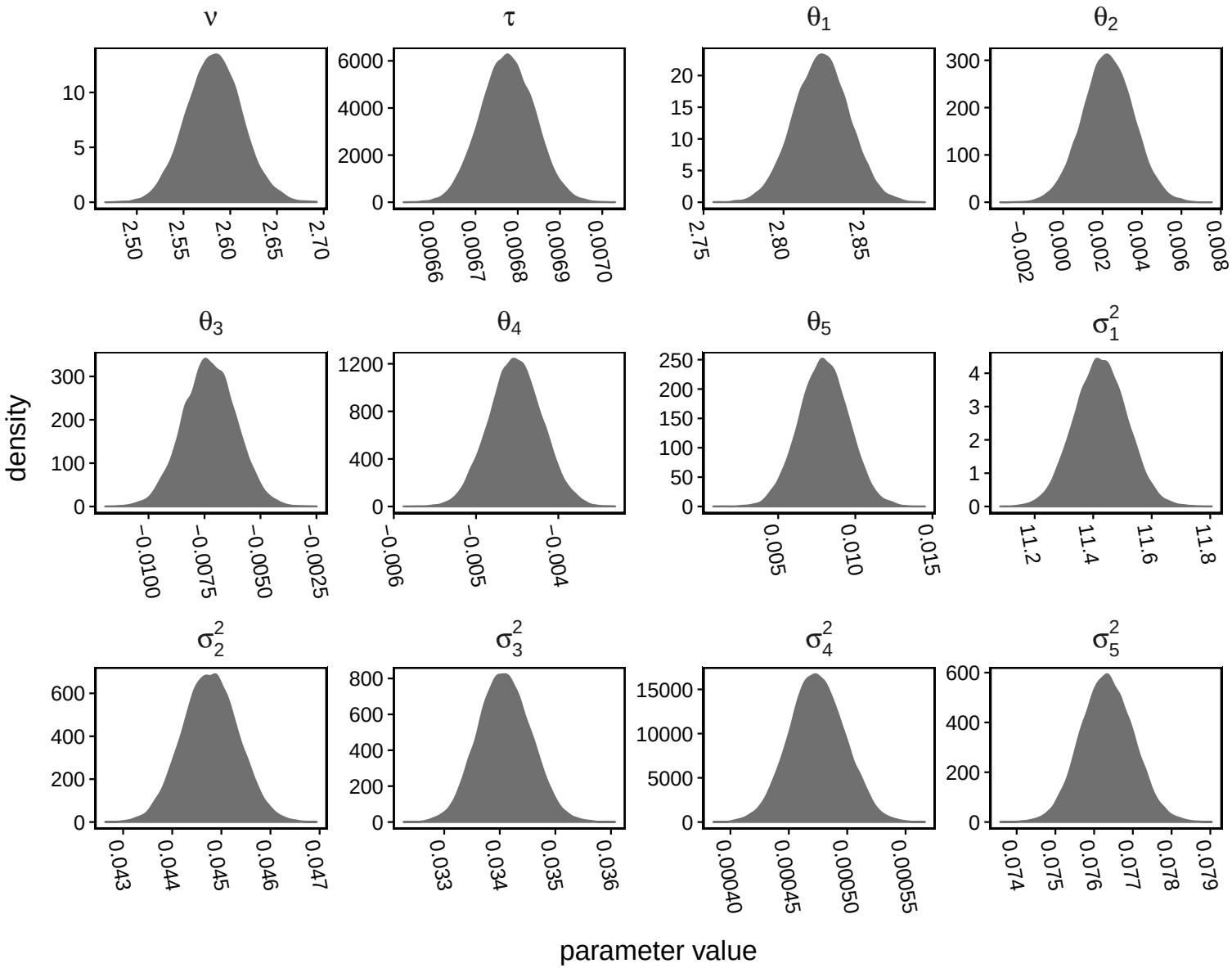


Analysis of Paschold et. al. (2012) data



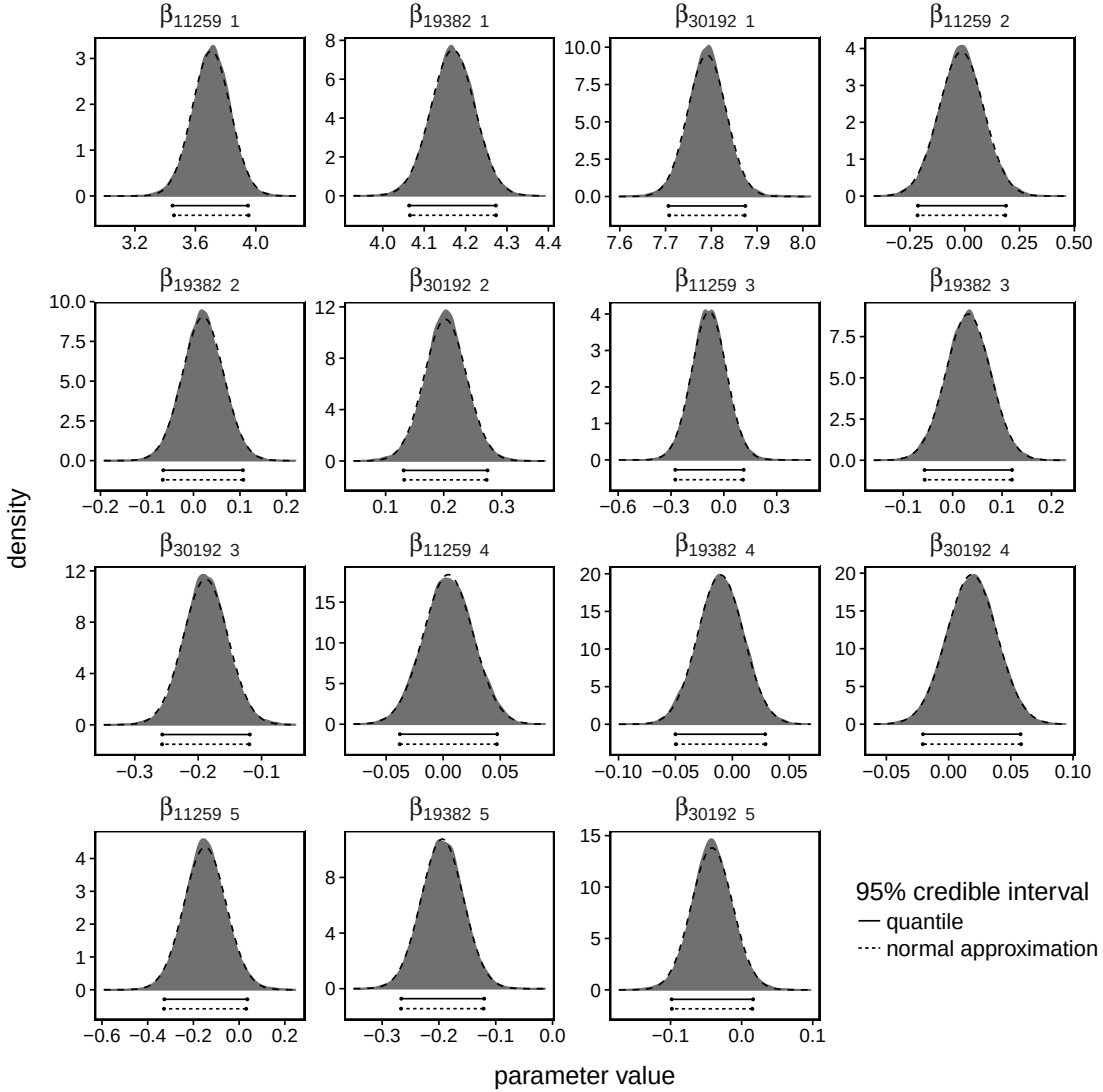
- $N = 16$ with 4 replicates/variety on 2 plates
  - varieties: B73, Mo17, B73$\times$Mo17, Mo17$\times$ B73
- $G = 39\,656$
- 21% of genes have mean counts less than 1
- 39% have mean counts less than 10
- count: median 37, mean 260, and max 38 010

Hyperparameter posterior



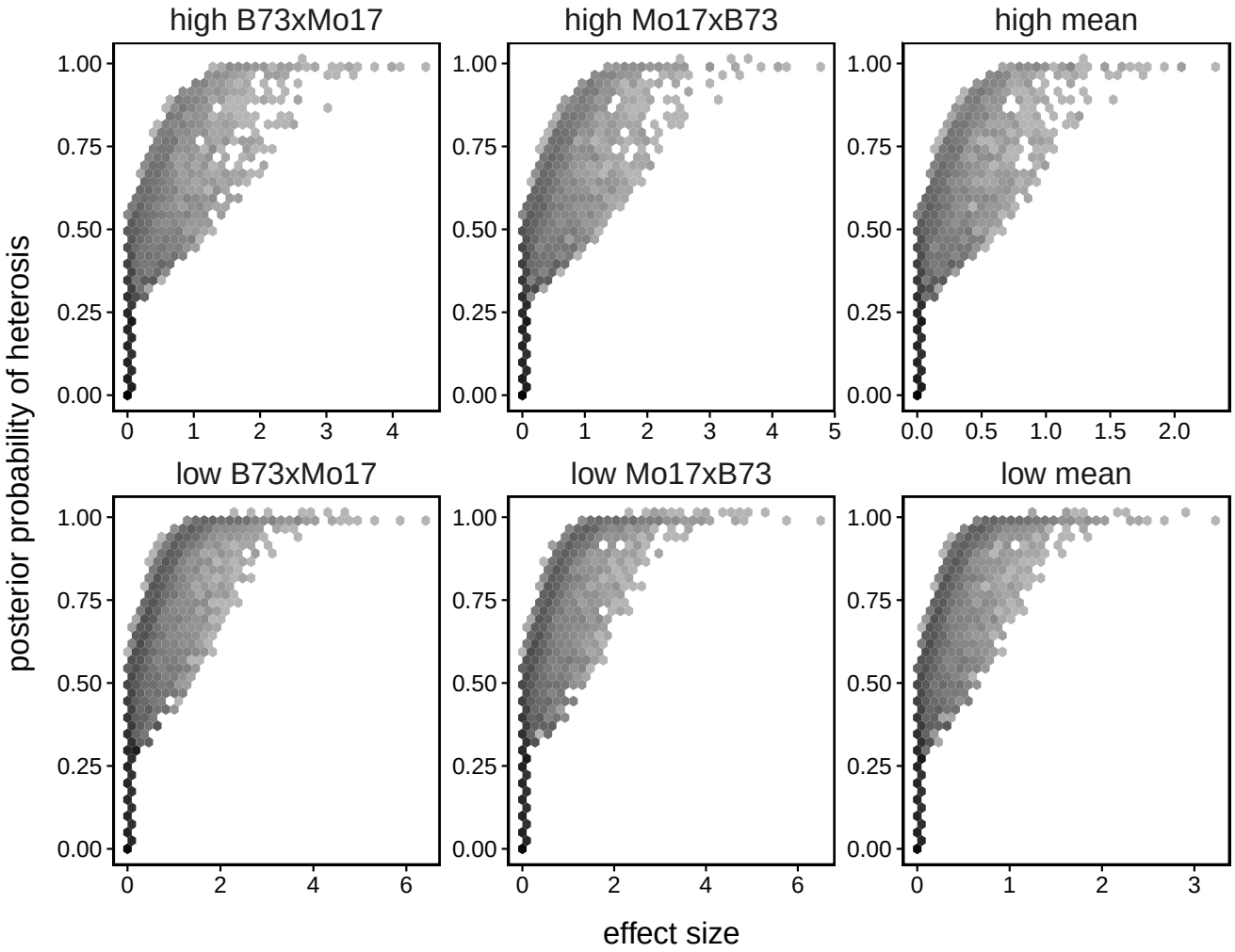
Gene-specific parameter posteriors

Compare posterior distribution (gray area) to normal-based approximation (black dashed line).

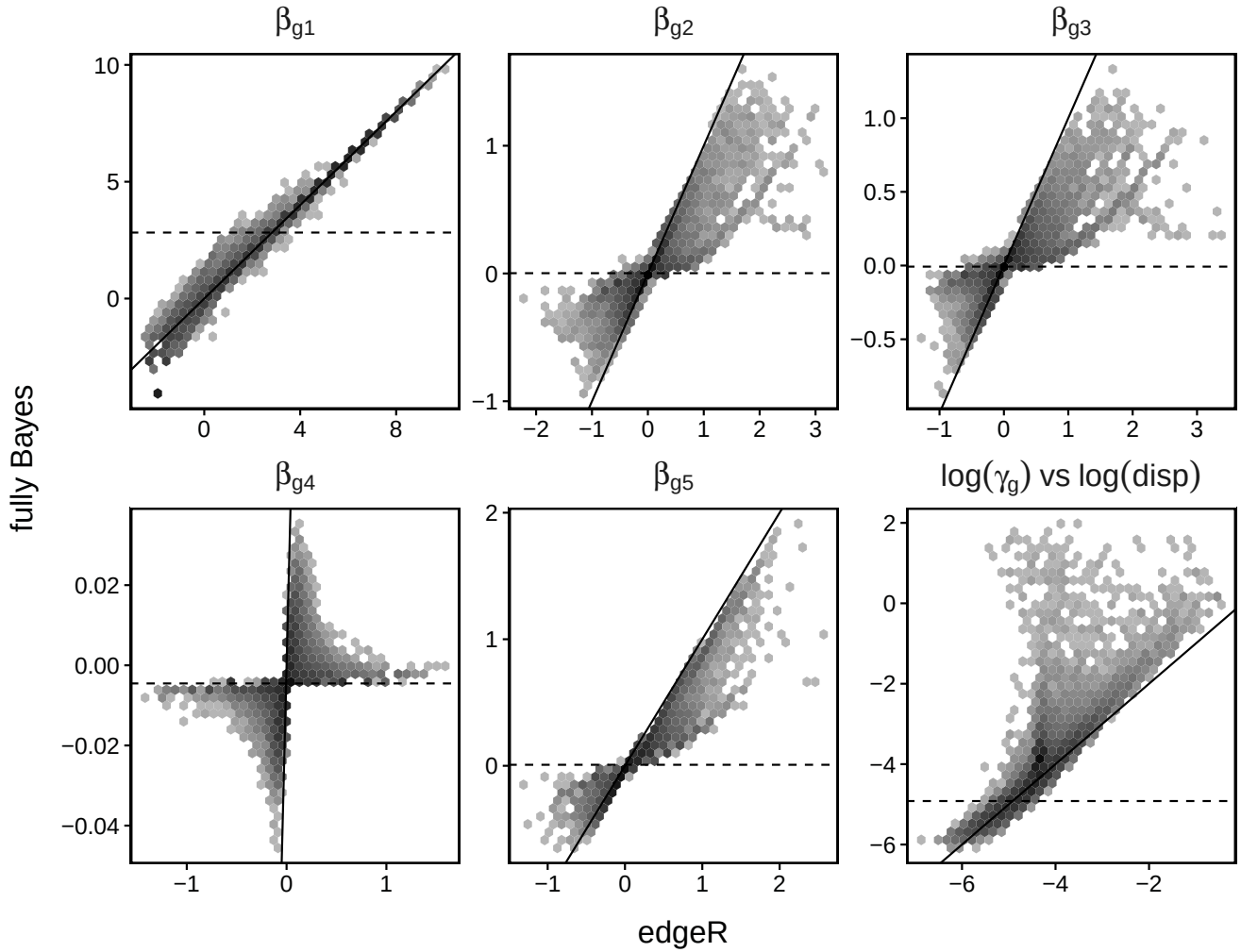


Smokestack plot

Effect size for HPH BM is the maximum of 0 and $\min(2\beta_{g2} + \beta_{g4}, 2\beta_{g3} + \beta_{g4})/\sqrt{\gamma_g}$.



Shrinkage



Summary

Material available at

- R package: `http://github.com/wlandau/fbseq`
- slide code: `https://github.com/jarad/ISU2016`
- slide pdf: `http://www.jarad.me/research/presentations.html`
- pre-print: `https://arxiv.org/abs/1606.06659`

Thank you!

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