

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

Jarad Niemi and Will Landau

Iowa State University

December 9, 2016

This research was supported by National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health and the joint National Science Foundation / NIGMS Mathematical Biology Program under award number R01GM109458. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the National Science Foundation.

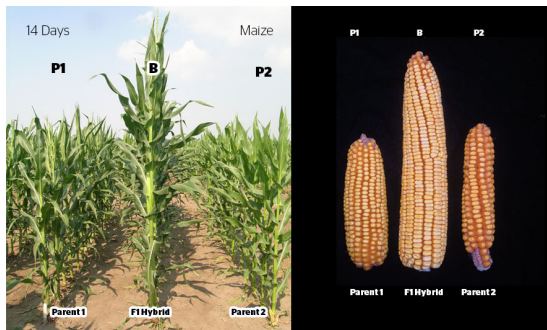
# Outline

- Background
  - Heterosis
  - RNAseq data
- Modeling
  - Composite null hypothesis
  - Hierarchical overdispersed count regression model
- Inference
  - Empirical Bayes
  - Fully Bayes on graphics processing units
    - Memory transfers
    - Random number generation
- Simulation studies
  - Credible interval coverage
  - Heterosis detection via ROC curves
- Real data analysis

# 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

# Hypotheses

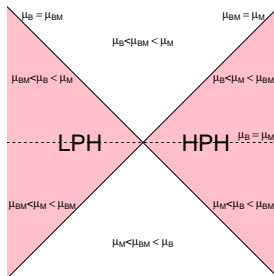
For a given gene, let

- $\mu_B$  : mean expression for B73 inbred parent,
- $\mu_M$  : mean expression for Mo17 inbred parent,
- $\mu_{BM}$ : mean expression for B73  $\times$  Mo17 F1 hybrid, and
- $\mu_{MB}$ : mean expression for Mo17  $\times$  B73 F1 hybrid.

We are interested in comparing hypotheses of the form

$$H_0 : \mu_{\min} < \mu_{BM} < \mu_{\max}, \quad H_{LPH} : \mu_{BM} < \mu_{\min}, \quad H_{HPH} : \mu_{\max} < \mu_{BM}$$

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



# 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.

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

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

- $g$  ( $g = 1, \dots, G$ ) identify the gene,
- $n$  ( $n = 1, \dots, N$ ) 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

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

where

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

# Hierarchical model

Recall

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

We construct a hierarchical model for both  $\gamma_g$  and  $\beta_g$  to borrow information across genes. Specifically, we assume

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

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

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

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



# Model matrix for our heterosis experiment

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

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

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

- $\beta_1$  is the parental mean
- $\beta_2$  is the half difference of hybrid mean vs M
- $\beta_3$  is the half difference of hybrid mean vs B
- $\beta_4$  is the half difference between hybrids
- $\beta_5$  is the flow cell block effect

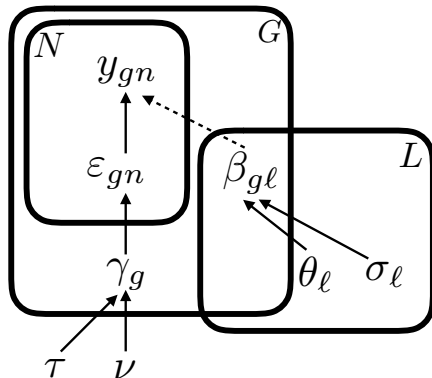
# Heterosis hypotheses

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

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



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

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

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

(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

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

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:

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

Sufficient “statistics”:

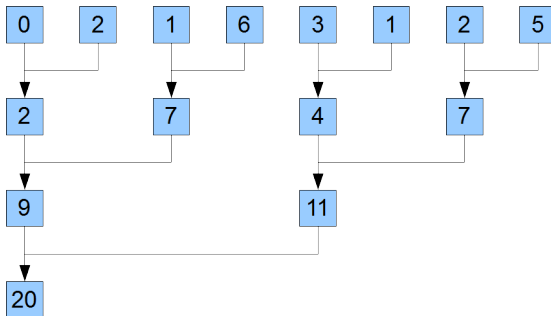
$$\begin{aligned}
 p(\tau | \dots) &\sim Ga(\tau | a', b') & (a', b') &= f_\tau(\gamma, \nu, a, b) \\
 p(\nu | \dots) &\sim p(\nu | d') I(0 < \nu < d) & d' &= f_\nu(\gamma, \tau, d) \\
 p(\theta_\ell | \dots) &\sim N(\theta_\ell | m'_\ell, C'_\ell) & (m'_\ell, C'_\ell) &= f_{\theta_\ell}(\beta_\ell,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

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  $\lceil G - 1 \rceil / \log_2(G)$



([https://scs.senecac.on.ca/~gpu610/pages/images/parallel\\_reduction.png](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  $\theta$  over the  $M$  iterations of chain  $c$ , calculate

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

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

Compute the Gelman-Rubin convergence diagnostic amongst  $C$  chains using

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

where

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

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



# Normal-based credible intervals

For the collection of parameters  $\psi$  and under regularity conditions, we have

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

as  $N \rightarrow \infty$  where  $\psi_0$  is the true value and  $I_N(\psi_0)$  is the Fisher information.

For any scalar parameter  $\theta$ , we have

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

and can construct normal-based credible intervals with

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

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

$$\begin{aligned} &P(\text{high parent heterosis for the B73} \times \text{Mo17 hybrid} | y) \\ &= P(2\beta_{g2} + \beta_{g4} > 0 \text{ and } 2\beta_{g3} + \beta_{g4} > 0 | y) \\ &\approx \frac{1}{M} \sum_{m=1}^M \mathbb{I}(2\beta_{g2}^{(m)} + \beta_{g4}^{(m)} > 0) \mathbb{I}(2\beta_{g3}^{(m)} + \beta_{g4}^{(m)} > 0) \end{aligned}$$

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`

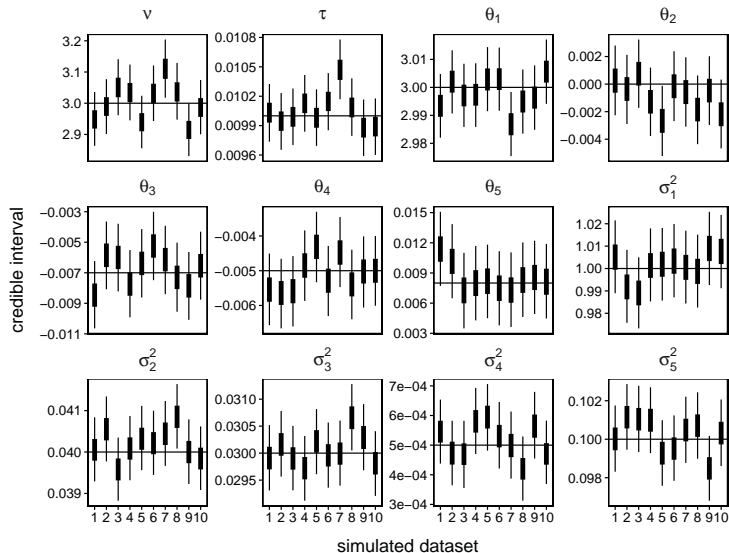
## high-parent_B73xMo17_1 high-parent_B73xMo17_2
##                      5                      6
```

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

# Simulation studies

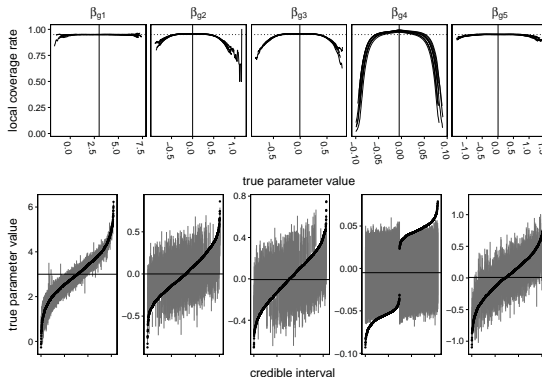
- Simulation model
  - Model: hierarchical count regression model with data-based hyperparameters
  - Simple: count regression model with sparsity in gene-specific parameters
  - edgeR: negative binomial model with data-based gene-specific parameters
- Inference
  - edgeR: non-hierarchical except for 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



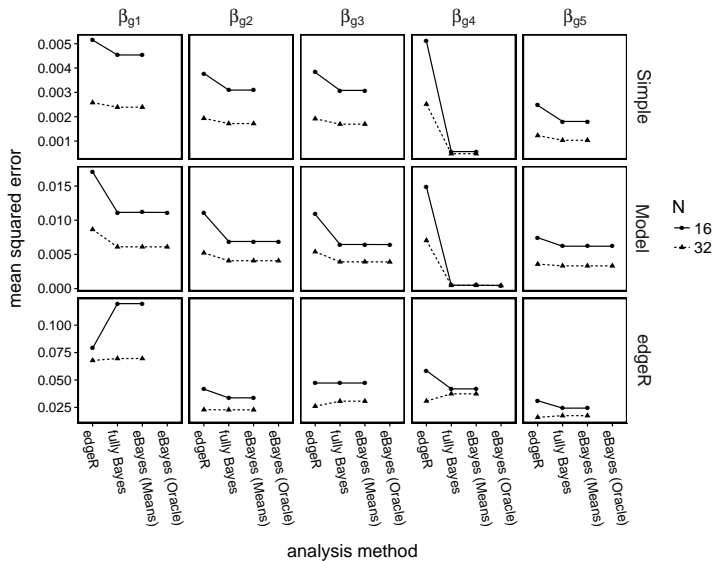
# Gene-specific parameter coverage

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

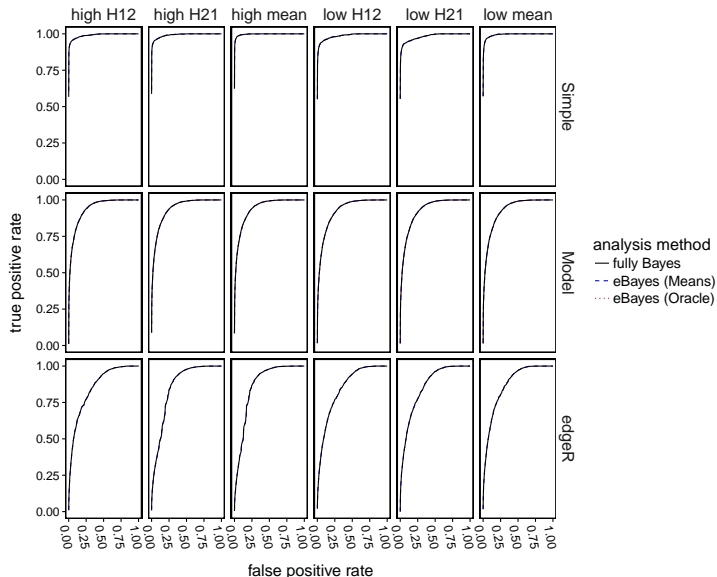


where the lower plot indicates that when the intervals miss, we are overshrinking.

# Mean squared error

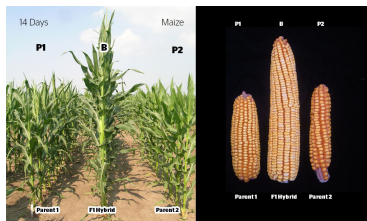


# ROC curves for heterosis detection



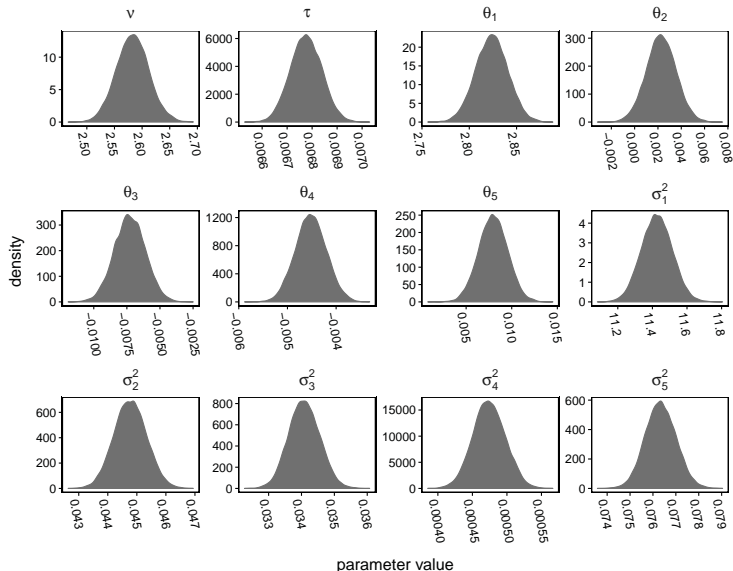


# Analysis of Paschold et. al. (2012) data



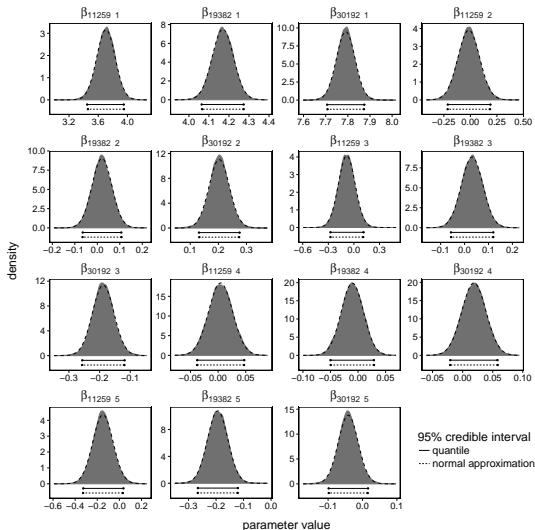
- $N = 16$  with 4 replicates/variety on 2 plates
  - varieties: B73, Mo17, B73 $\times$ Mo17, Mo17 $\times$  B73
- $G = 39\,656$
- 21% of genes have mean counts less than 1
- 39% have mean counts less than 10
- count: median 37, mean 260, and max 38 010

# Hyperparameter posterior



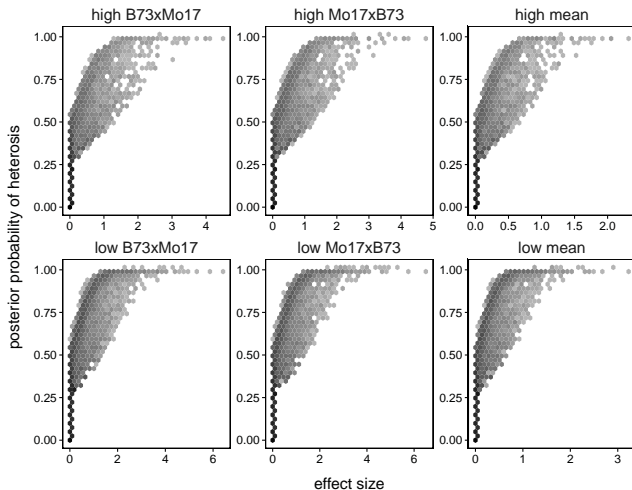
# Gene-specific parameter posteriors

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

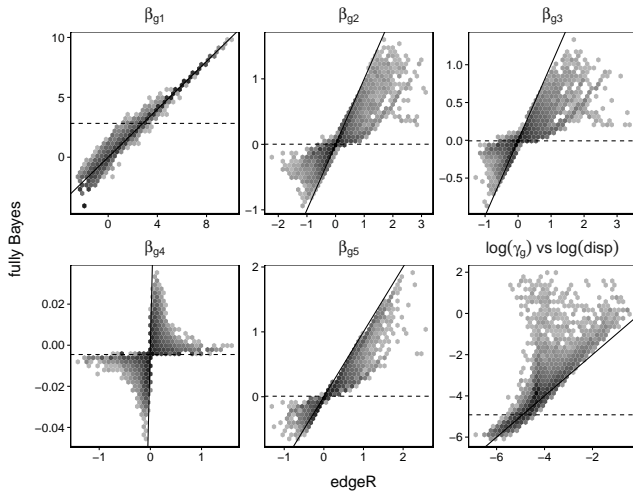


# Smokestack plot

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

- Introduced a hierarchical overdispersed count regression model and
- a GPU-implementation of a fully Bayesian analysis.

These slides are available

- <https://github.com/jarad/ISU2016>
- <http://www.jarad.me/research/presentations.html>

# Thank you!

# References

- Carvalho, C. M., Polson, N. G., and Scott, J. G. (2010). The horseshoe estimator for sparse signals. *Biometrika* 97(2) 465–480
- Gelman, A. (2006) Prior distributions for variance parameters in hierarchical models (comment on article by Browne and Draper). *Bayesian analysis*, 1(3), 515–534.
- Gelman, A., Hill, J., and Yajima, M. (2012) Why we (usually) don't have to worry about multiple comparisons. *Journal of Research on Educational Effectiveness*, 5(2), 189–211.
- Hans, C. (2009). Bayesian lasso regression. *Biometrika*, 96(4), 835–845.
- Lee, A., Yau, C., Giles, M. B., Doucet, A., and Holmes, C. C. (2010). On the utility of graphics cards to perform massively parallel simulation of advanced Monte Carlo methods. *Journal of computational and graphical statistics*, 19(4), 769–789.
- Lithio, A., and Nettleton, D. (2015). Hierarchical modeling and differential expression analysis for rna-seq experiments with inbred and hybrid genotypes. *Journal of Agricultural, Biological, and Environmental Statistics*, 20(4), 598–613.
- Liu, Fangfang, Chong Wang, and Peng Liu. (2015) A Semi-parametric Bayesian Approach for Differential Expression Analysis of RNA-seq Data. *Journal of Agricultural, Biological, and Environmental Statistics* 20, no. 4 : 555–576.
- Park, T., and Casella, G. (2008). The Bayesian lasso. *Journal of the American Statistical Association*, 103(482), 681–686.
- Paschold, A., Jia, Y., Marcon, C., Lund, S., Larson, N.B., Yeh, C.T., Ossowski, S., Lanz, C., Nettleton, D., Schnable, P.S. and Hochholdinger, F., (2012) Complementation contributes to transcriptome complexity in maize (*Zea mays* L.) hybrids relative to their inbred parents. *Genome research*, 22(12), pp.2445–2454.
- Suchard, M. A., Wang, Q., Chan, C., Frelinger, J., Cron, A., and West, M. (2010). Understanding GPU programming for statistical computation: Studies in massively parallel massive mixtures. *Journal of Computational and Graphical Statistics*, 19(2), 419–438.