Detecting Rare and Faint Signals via Thresholding Maximum Likelihood Estimators

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A joint work with Yumou Qiu and Dan Nettleton

Detecting Rare and Faint Nonzero Means

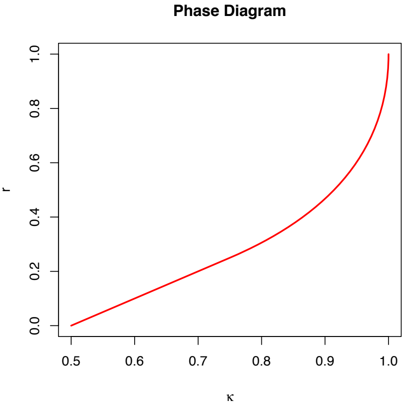
- $X_1, \cdots, X_n \overset{i.i.d.}{\sim} N(\mu, I_{p\times p})$, p dimensional random vectors
- $\mu = \mathrm{E}(X_i) = (\mu_1, \cdots, \mu_p)'$
- Donoho and Jin (2004) test for zero mean against rare and faint H_a

$$H_0 : \mu_j = 0 \text{ for all } j \text{ vs. } H_a : \mu_j \sim (1-\epsilon)\nu_0 + \epsilon\nu_{\mu_a}$$

- Rareness: few dimensions with nonzero mean, $\epsilon = p^{-\kappa}$, $\kappa \in (1/2, 1)$
- Faintness: weak nonzero mean, $\mu_a = \sqrt{(2r\log p)/n}$, $r \in (0,1)$
- Most challenging situation for signal detection

Optimal Detection Boundary

$$\mathrm{DB}(\kappa) = \begin{cases} \kappa - 1/2 & \text{if } 1/2 < \kappa \leq 3/4, \\ (1 - \sqrt{1-\kappa})^2 & \text{if } 3/4 < \kappa < 1, \end{cases}$$



- Ingster (1997)
- $r < \mathrm{DB}(\kappa)$: Type I Error + Type II Error → 1 for ANY TEST
- $r > \mathrm{DB}(\kappa)$: there exists a test such that Type I Error + Type II Error → 0

Higher Criticism (HC) test

- Donoho and Jin (2004) proposed Higher Criticism (HC) test
- $\{p_{(j)}\}$: ordered p-values for testing each dimension

$$HC^* = \max_{1 \le j \le p/2} \sqrt{p}[j/p - p_{(j)}]/[p_{(j)}(1 - p_{(j)})]^{1/2}$$

- Reject H_0 if $HC^* > \sqrt{2 \log \log p}$
- HC test is able to attain the optimal detection boundary

Further Works on Testing Means

- Hall and Jin (2008, 2010): data dependence and Innovated HC test
  - Apply HC on $\widehat{\Sigma}^{-1} X_i$
- Zhong, Chen and Xu (2013): L_2 thresholding test, more powerful
  - $M_n(s) = \sum_{j=1}^{p} n(\bar{X}_j / s_j)^2 \mathbf{I}\left(|\bar{X}_j|/s_j > \sqrt{(2s \log p)/n}\right)$
  - $\mathcal{M}_n = \max_{0<s<1} \{M_n(s) - \mu_n(s)\}/\sigma_n(s)$
- Chen, Li and Zhong (2016): thresholding with data transformation
  - Apply L_2 thresholding on $\widehat{\Sigma}^{-1} X_i$
- Fan (1996): goodness-of-fit test

Settings of the Problem

- Collect p responses variables from n observations under m treatments
- y_{ij}: the value of the jth response variable in the ith observation
- $i = 1, \cdots, n$ and $j = 1, \cdots, p$
- Let z_i be the explanatory variables for the ith observation
- $z_i = (z_{i,1}, \cdots, z_{i,m})'$
- m is the number of explanatory variables, **fixed**

Generalized Linear Models

- Suppose y_{ij} is within the exponential family
- $\mu_{ij} = \mathrm{E}(y_{ij})$ and ϕ_j is the dispersion parameter
- Link function: $g(\mu_{ij}) = \eta_{ij} = z_i' \beta_j$
- $\beta_j = (\beta_{j,1}, \cdots, \beta_{j,m})'$: treatment effect for the jth response variable

Any Signal in the Regression Coefficient?

- Interested in testing the hypotheses

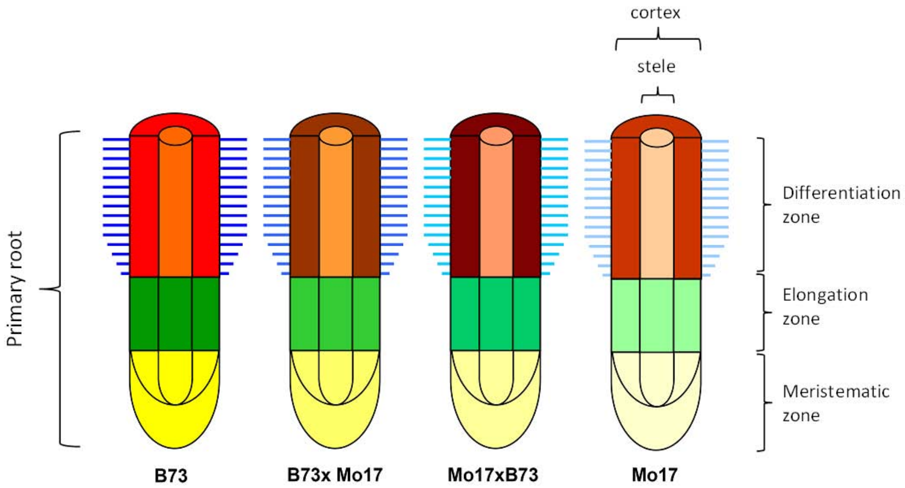
$$H_0 : D\beta_j = 0 \text{ for all } j \quad \text{vs.} \quad H_a : \text{not all the } D\beta_j = 0.$$

- $D_{d\times m}$ is a known matrix

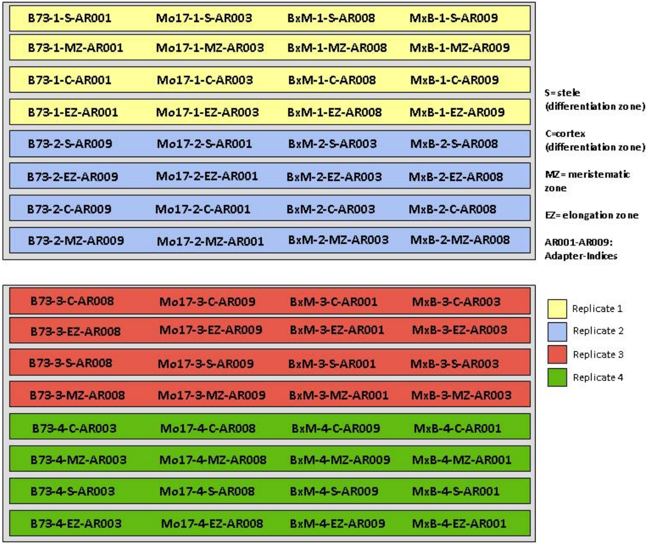
Maize RNA-seq Experiment

- Maize gene expressions are measured by RNA-Seq
- 4 genotypes: B73, Mo17, B73×Mo17 (BM) and Mo17×B73 (MB)
- 4 tissues: cortex, stele, elongation zone, meristematic zone
- 4 barcodings: AR001, AR003, AR008 and AR009
- 4 replications

Genotypes and Tissues of Corn Root



Strip-plot Experimental Design



B73-1-S-AR001	Mo17-1-S-AR003	BxM-1-S-AR008	MxB-1-S-AR009
B73-1-MZ-AR001	Mo17-1-MZ-AR003	BxM-1-MZ-AR008	MxB-1-MZ-AR009
B73-1-C-AR001	Mo17-1-C-AR003	BxM-1-C-AR008	MxB-1-C-AR009
B73-1-EZ-AR001	Mo17-1-EZ-AR003	BxM-1-EZ-AR008	MxB-1-EZ-AR009
B73-2-S-AR009	Mo17-2-S-AR001	BxM-2-S-AR003	MxB-2-S-AR008
B73-2-EZ-AR009	Mo17-2-EZ-AR001	BxM-2-EZ-AR003	MxB-2-EZ-AR008
B73-2-C-AR009	Mo17-2-C-AR001	BxM-2-C-AR003	MxB-2-C-AR008
B73-2-MZ-AR009	Mo17-2-MZ-AR001	BxM-2-MZ-AR003	MxB-2-MZ-AR008

S=stele (differentiation zone)

C=cortex (differentiation zone)

MZ= meristematic zone

EZ= elongation zone

AR001-AR009: Adapter-Indices

B73-3-C-AR008	Mo17-3-C-AR009	BxM-3-C-AR001	MxB-3-C-AR003
B73-3-EZ-AR008	Mo17-3-EZ-AR009	BxM-3-EZ-AR001	MxB-3-EZ-AR003
B73-3-S-AR008	Mo17-3-S-AR009	BxM-3-S-AR001	MxB-3-S-AR003
B73-3-MZ-AR008	Mo17-3-MZ-AR009	BxM-3-MZ-AR001	MxB-3-MZ-AR003
B73-4-C-AR003	Mo17-4-C-AR008	BxM-4-C-AR009	MxB-4-C-AR001
B73-4-MZ-AR003	Mo17-4-MZ-AR008	BxM-4-MZ-AR009	MxB-4-MZ-AR001
B73-4-S-AR003	Mo17-4-S-AR008	BxM-4-S-AR009	MxB-4-S-AR001
B73-4-EZ-AR003	Mo17-4-EZ-AR008	BxM-4-EZ-AR009	MxB-4-EZ-AR001

🟨 Replicate 1

🟦 Replicate 2

🟥 Replicate 3

🟩 Replicate 4

Negative-Binomial Model

- Consider the tissue-specific analysis for the stele tissue
- Denote $Y_j = (y_{1,j}, \cdots, y_{16,j})$ to be the expression level of the jth gene
- NB model for $y_{i,j}$ with mean $\mu_{i,j}$ and dispersion parameter ϕ_j such that

$$\log(\mu_{i,j}) = \nu_j + X'_{g,i}\alpha_j + X'_{r,i}\xi_j + X'_{b,i}\gamma_j,$$

- $\alpha_j, \xi_j, \gamma_j$: treatment effects for genotype, replication and barcoding
- Satisfying $\alpha_{j,4} = \beta_{j,4} = \gamma_{j,4} = 0$, baseline

Hypotheses

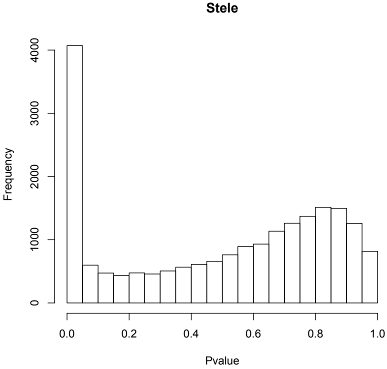
- Any of the genes is differentially expressed across different genotypes?
- Genotype effect:

$$
\begin{aligned}
&H_0 : \alpha_{1,j} = \alpha_{2,j} = \alpha_{3,j} = 0 \ \text{ for all } j \ \text{ vs.} \\
&H_a : \text{at least one component of } \alpha_j \text{ not equal to 0 for some } j.
\end{aligned}
$$

- Difference between B73×Mo17 (BM) and Mo17×B73 (MB):

$$H_0 : \alpha_{2,j} = \alpha_{3,j} \ \text{ for all } j \ \text{ vs. } \ H_a : \alpha_{2,j} \neq \alpha_{3,j} \ \text{ for some } j.$$

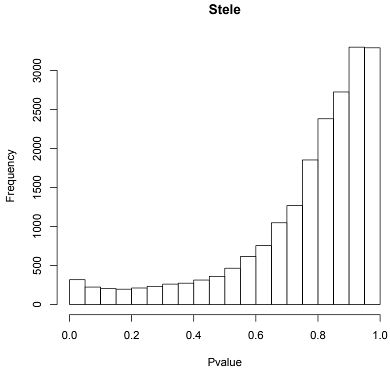
P-Value of Overall Genotype Effect



- Wald's Test for each gene
- Many small P-values
- Strong evidence in favor of H_a
- Some of the genes are differentially expressed under some genotypes

P-Value of the Difference Between BM and MB

How to detect rare and faint genetic signals in RNA-seq data?



- Few small P-values
- Not have strong evidence to reject H_0 based on this histogram
- If H_a is true, few genes have different BM and MB genetic effects

Sparse and Weak H_a

Consider the hypotheses with rare and faint signals

$$H_0 : \beta_j = \beta_{j,0} \ \text{ such that } D\beta_{j,0} = 0 \text{ for all } j \ \text{ vs.}$$

$$H_a : \beta_j \sim (1-\epsilon)\nu_{\beta_{j,0}} + \epsilon\nu_{\beta_{j,0}+\beta_{j,a}} \ \text{ for all } j,$$

- For $x \in \mathbb{R}^m$, ν_x denotes the point mass distribution on x
- Under H_a, β_j comes from a binary super-population
- $\epsilon = p^{-\kappa}$ for $\kappa \in (1/2, 1)$, κ specify the sparsity
- $\beta_{j,a} = r_j\sqrt{2(\log p)/n}$ for $r_j \in (0,1)^m$ and $Dr_j \neq 0$
- $\{r_j\}$ specify the signal strength

Regularize MLEs by Thresholding

- $(\hat{\beta}_j', \hat{\phi}_j)'$: MLEs to the jth response variable
- $\hat{\beta}_j = (\hat{\beta}_{j,1}, \cdots, \hat{\beta}_{j,m})'$ the estimated treatment effects
- $D\hat{\beta}_j$ MLE of $D\beta_j$
- Most of the responses have no signal
- Truncate those small $\|D\hat{\beta}_j\|$ to 0 and keep the large ones

Thresholding Statistic

- Let nI_j be the Fisher Information matrix of β_j
- $\hat{I}_j = I_j(\hat{\beta}_j, \hat{\phi}_j)$ is the estimated Fisher Information matrix
- $\hat{V}_j/n = D\hat{I}_j^{-1}D'/n$ is the estimated asymptotic variance of $D\hat{\beta}_j$
- For a constant $s \in (0,1)$, the thresholding statistic is

$$T_n(s) = \sum_{j=1}^{p} n(D\hat{\beta}_j)'\hat{V}_j^{-1}(D\hat{\beta}_j)\mathbf{I}\left(\|\hat{V}_j^{-1/2}D\hat{\beta}_j\| > \sqrt{(2s\log p)/n}\right)$$

Moderate Deviation Expansion for MLE

Lemma 1. *Suppose $X_1, \cdots, X_n$ are independent with pdf $f_i(x_i, \theta)$*

- *θ is m dimensional unknown parameter, θ_0 is the truth*
- *$\hat{\theta}$ be the MLE of θ*
- *Under some regularity conditions, for $w_n \ll n^{1/6}$*
    - The 2rd derivative of $\log f_i(x_i, \theta)$ is Lipschitz continuous
    - MGFs of the 1st and 2rd derivative of $\log f_i(X_i, \theta)$ exist around 0

$$P\left(|\sqrt{n\hat{I}}(\hat{\theta} - \theta_0)| \geq w_n\right) = P\left(|N(0, I_m)| \geq w_n\right)(1 + O(w_n^3/\sqrt{n})).$$

Moderate Deviation Expansion for MLE

- Cramér moderate deviation for MLE under non identically distr data
- Tail distribution of MLEs can be approximated by that of $N(0, I_m)$
- For i.i.d. data, Inglot and Kallenberg (2003)

$$\lim_{n\to\infty} w_n^{-2} \log\left\{P\left(\sqrt{n}|I_\theta^{1/2}(\hat{\theta}-\theta^0)| \geq w_n\right)\right\} = -1/2$$

- We provide the error rate of the normal approximation
- Needed for the analysis of the thresholding approach

Dependence among Responses

- Let $Y_i = (y_{i1}, \cdots, y_{ip})'$ and $\mathcal{F}_a^b(Y_i) = \sigma\{Y_{ij} : a \leq j \leq b\}$
- ρ-mixing coefficients: $\rho_i(k) = \sup_{m \in \mathbb{Z}} \rho\{\mathcal{F}_{-\infty}^m(Y_i), \mathcal{F}_{m+k}^{\infty}(Y_i)\}$.
- Assume Y_i is a ρ-mixing sequence, and

$$\rho_i(k) \leq C\alpha^k \quad \text{for a constant } \alpha \in (0,1)$$

- Only require the condition holds for some ordering of response variables

Mean and Variance of $T_n(s)$ under H_0

- Tail distribution of $\sqrt{n}\hat{V}_j^{-1/2} D\hat{\beta}_j$ be approximated by that of $N(0, I_d)$
- Write $\lambda_n(s) = 2s\log p$, assuming $\log p = o(n^{1/3})$
- $\mu_0(s) = p\mathrm{E}\{\chi_d^2 \, \mathbf{I}(\chi_d^2 \geq \lambda(s))\}$
- $\sigma_0^2(s) = p\mathrm{Var}\{\chi_d^2 \, \mathbf{I}(\chi_d^2 \geq \lambda(s))\}$
- $\mathrm{E}\{T_n(s)|H_0\} = \mu_0(s)\{1 + O(\lambda_n(s)^{3/2}/\sqrt{n})\}$
- $\mathrm{Var}\{T_n(s)|H_0\} = \sigma_0^2(s)\{1 + o(1)\}$

Single Level Thresholding

Theorem 1. *Under H_0 and some regularity conditions, if* $\log p = o(n^{1/3})$,

$$\frac{T_n(s) - \mathrm{E}\{T_n(s)|H_0\}}{\sqrt{\mathrm{Var}\{T_n(s)|H_0\}}} \xrightarrow{d} N(0,1) \text{ as } n, p \to \infty.$$

- Reject H_0 if $T_n(s) - \mu_0(s) > \sigma_0(s) z_\alpha$

Multi-level Thresholding

- Standardized thresholding statistic

$$\hat{T}_n(s) = \sigma_0(s)^{-1}\{T_n(s) - \hat{\mu}(s)\}$$

- For a small positive constant ω, maximize $\hat{T}_n(s)$ over $\mathcal{S}_n$

$$\mathcal{S}_n = \{s_j : s_j = n(D\hat{\beta}_j)'\hat{V}_j^{-1}(D\hat{\beta}_j)/(2\log p), s_j \leq 1 - \omega, j \leq p\}$$

- Let $\mathcal{T}_n = \max_{s \in \mathcal{S}_n} \hat{T}_n(s)$

Multi-level Thresholding Test (MTT)

Theorem 2. *Under* H_0*, some regularity conditions and* $\log p = o(n^{1/3})$

$$P\left(a_p \mathcal{T}_n - b_p(\omega) \leq x\right) \to \exp\{-\exp(-x)\}$$

where a_p *and* $b_p(\omega)$ *are multi-*$\log(p)$ *terms.*

- g_α: the upper α quantile of Gumbel distribution
- Reject H_0 if $\mathcal{T}_n > a_p^{-1}(g_\alpha + b_p(\omega))$

Power Analysis

$$H_0 : \beta_j = \beta_{j,0} \text{ such that } D\beta_{j,0} = 0 \text{ for all } j \text{ vs.}$$

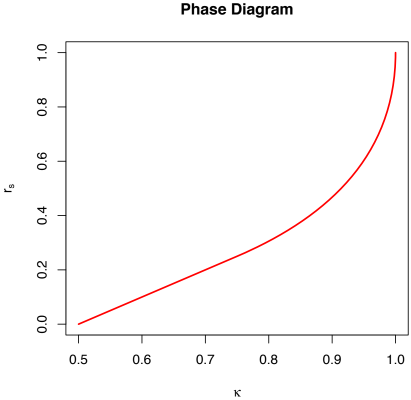
$$H_a : \beta_j \sim (1-\epsilon)\nu_{\beta_{j,0}} + \epsilon\nu_{\beta_{j,0}+\beta_{j,a}} \text{ for all } j,$$

- $\beta_{j,a} = r_j\sqrt{2(\log p)/n}$ and $\epsilon = p^{-\kappa}$
- the standardized signal strength:

$$r_s = \max_j r_j' D' V_j^{-1} D r_j \text{ where } V_j = D I_j^{-1} D'$$

Detection Boundary of Multi-level Thresholding (MTT)

$$\mathrm{DB}(\kappa) = \begin{cases} \kappa - 1/2 & \text{if } 1/2 < \kappa \le 3/4, \\ (1 - \sqrt{1-\kappa})^2 & \text{if } 3/4 < \kappa < 1, \end{cases}$$



- For type I error rates $\alpha_n \to 0$ slowly as $n \to \infty$
- If $r_s < \mathrm{DB}(\kappa)$, power $\to 0$
- If $r_s > \mathrm{DB}(\kappa)$, power $\to 1$

Detection Lower Bound - linear model

- Linear regression model

$$y_{ij} = z_i'\beta_j + \varepsilon_{ij} \ \text{ for } \ \varepsilon_{ij} \overset{i.i.d.}{\sim} N(0, \sigma^2).$$

- Design matrix $Z = (z_1, \cdots, z_n)'$
- $r_s = \lim\limits_{n \to \infty} \max\limits_j r_j' D' \{D(Z'Z)^{-1}D'\}^{-1} D r_j / (n\sigma^2)$
- If $r_s < \mathrm{DB}(\kappa)$, Type I Error + Type II Error $\to 1$ for ANY TEST
- MTT can attain the optimal detection boundary

Detection Lower Bound - general models

- $I_\beta = -\lim_{n\to\infty}\sum_{i=1}^{n} \mathrm{E}\frac{\partial^2}{\partial\beta\partial\beta'}\log f(y_{ij}; z_i,\theta)/n$
- $r_0 = \max_j r_j' I_\beta r_j$
- $r_s = \max_j r_j' D' V_j^{-1} D r_j$ for $V_j = D I_j^{-1} D'$
- If $r_0 < \mathrm{DB}(\kappa)$, Type I Error $+$ Type II Error $\to 1$ for ANY TEST
- $r_0 \geq r_s$ with equality if ϕ_j is known and D takes the identity matrix
- MTT can attain the optimal detection boundary under this case

Signal Identification

- Which genes are differentially expressed?
- Multiple testing: $H_{j,0} : D\beta_j = 0$ vs. $H_{j,a} : D\beta_j \neq 0$
- FDP: proportion of falsely rejected among all rejected nulls
- FDR: expectation of FDP
- Exceedance FDP rate: probability that FDP exceeds a specific value

Step-down Procedure

- Obtain p-value of Wald test for each dimension
- $\pi(j)$: the dimension label of the jth smallest p-value
- $W_j = \{\pi(j), \pi(j+1), \cdots, \pi(p)\}$
- $H_{W_j,0} : D\beta_\ell = 0$ for all $\ell \in W_j$
- MTT on $H_{W_j,0}$ for each W_j at level α until no rejection
- $J = \min\{j : \mathcal{T}(W_j) \le a_{p-j+1}^{-1}(g_\alpha + b_{p-j+1}(\omega))\}$
- Step-down procedure rejects the first $J-1$ significant dimensions

Step-down Procedure + Augmentation

- Augment the rejection set of the step-down procedure by rejecting the next $\lfloor (J-1)c/(1-c) \rfloor$ significant dimensions
- Genovese and Wasserman (2006): maximum test for $H_{W_j,0}$
- Let $J^* = \min\{p, \lfloor (J-1)/(1-c) \rfloor\}$
- Reject the first J^* significant dimensions

FDP Control and Power

- $p - p_0$: total number of signals; S: true positives
- Standardized signal strength homogenous across dimensions

Theorem 3. *Under* H_a*, some regularity conditions and* $\log p = o(n^{1/3})$

- *Proposed procedure:* $P(\mathrm{FDP} > c) \leq \alpha$ *as* $n, p \to \infty$
- $S_{GW}/(p - p_0) \xrightarrow{p} 0$ *when* $r_s < 1$
- $S_{GW}/(p - p_0) \xrightarrow{p} 1$ *at rate* $p^{-(\sqrt{r_s} - \sqrt{\kappa})^2 + o(1)}$ *when* $r_s > 1$
- $S_{prop}/(p - p_0)$, $S_{BH}/(p - p_0)$ *converge to* 1 *at rate* $p^{-(\sqrt{r_s} - \sqrt{\kappa})^2 + o(1)}$

Simulation

$$H_0 : \beta_{j1} = \beta_{j2} \text{ for all } j \quad \text{vs.} \quad H_a : \beta_{j2} \overset{i.i.d.}{\sim} (1-\epsilon)\nu_{\beta_{j1}} + \epsilon\nu_{\beta_{j1}+\beta_a}$$

- Balanced designs with two treatments, $z_i = (1,0)'$ or $(0,1)'$
- $n = 40$, $p = 100, 400, 700, 1000$, nominal size 5%
- $\epsilon = p^{-\kappa}$ and $\beta_a = \sqrt{(2r_a \log p)/n}$
- $\kappa = 0.6$ $(7, 11, 14$ and $16)$ and 0.55 $(8, 15, 19$ and $22)$
- r_a was chosen differently to make $r_s \in (0,1)$
- $\beta_{11}, \cdots, \beta_{p1}$ were randomly generated, and kept fixed in simulation

Poisson and Binomial Regression

Poisson regression

- Response y_{ij} follow Poisson distribution with mean μ_{ij}
- Log link: $\log(\mu_{ij}) = z_i'\beta_j$ and $\phi = 1$

Binomial regression

- Response y_{ij} follow Binomial(m_{ij}, p_{ij})
- Logistic link: $p_{ij} = \exp(z_i'\beta_j)/\{\exp(z_i'\beta_j) + 1\}$
- m_{ij} is randomly chosen from the integers between 20 and 40.

Negative Binomial Regression

- $\mathrm{E}(y_{ij}) = \mu_{ij}$ and $\mathrm{Var}(y_{ij}) = \mu_{ij} + \mu_{ij}^2/\phi_j$
- Log link: $\log(\mu_{ij}) = z_i'\beta_j$
- The dispersion parameter $\phi_j \overset{i.i.d.}{\sim} \mathrm{Unif}(3,5)$
- The MLE $\hat{\phi}_j$ over estimates $\phi_j \Rightarrow$ size distortion
- Use parametric bootstrap to correct the bias of $\hat{\phi}_j$

Logistic-Normal Mixed Regression

- Single normal random effect

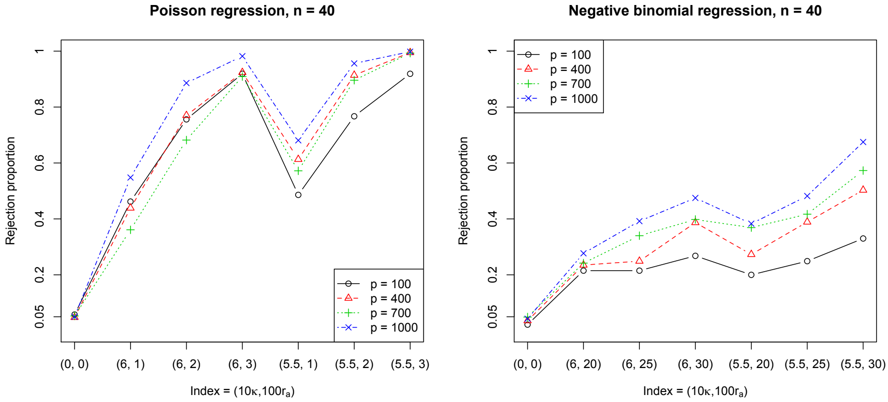
$$y_{1ij} \sim \text{Bin}(m_{1ij}, p_{1ij}) \quad \text{and} \quad y_{2ij} \sim \text{Bin}(m_{2ij}, p_{2ij}),$$

$$\text{Logit}(p_{1ij}) = \beta_{1j} + \gamma_{ij} \quad \text{and} \quad \text{Logit}(p_{2ij}) = \beta_{2j} + \gamma_{ij}$$

- $\gamma_{ij} \sim N(0, \sigma_j^2)$ for $i = 1, \cdots, n/2$, $\sigma_j = 0.1$
- m_{1ij}, m_{2ij} is randomly chosen from the integers between 20 and 40.

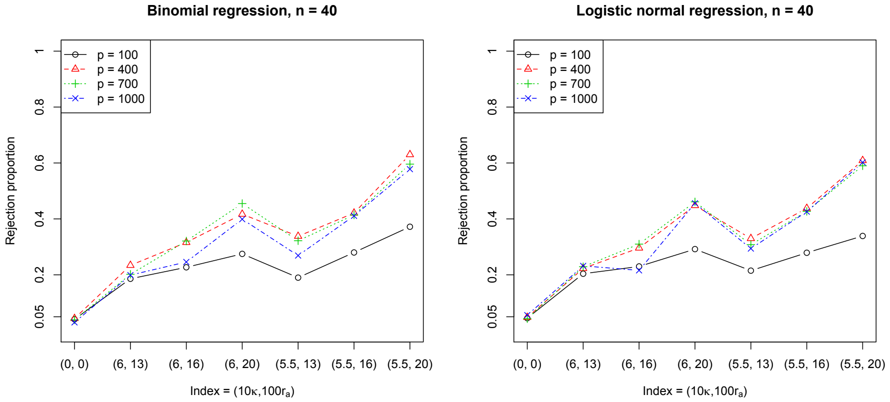
Poisson and Negative Binomial Regression

Under H_0, $\{\beta_{j1}\}_{j=1}^{p} \overset{i.i.d.}{\sim} \text{unif}(2,5)$



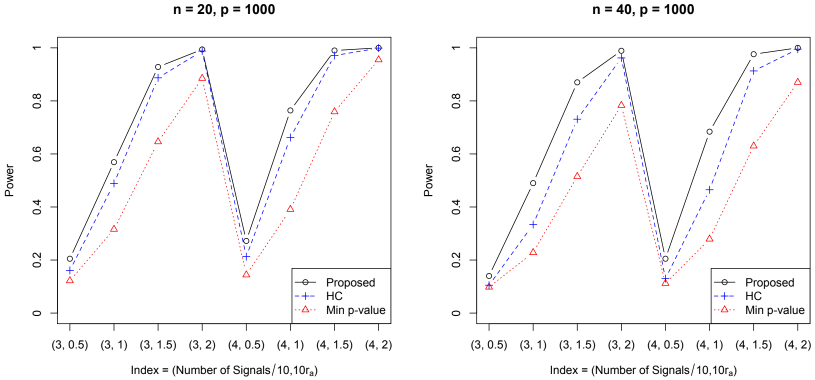
Binomial and Logistic-Normal Regression

Under H_0, $\{\beta_{j1}\}_{j=1}^{p} \overset{i.i.d.}{\sim} \text{unif}(-1, 2.5)$



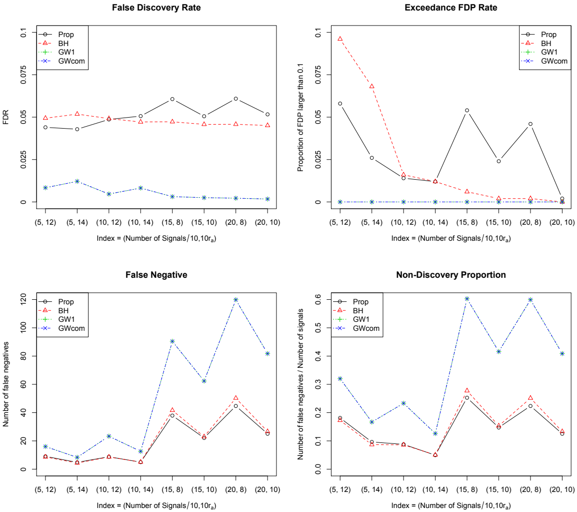
Power Comparison

multi-level thresholding, HC and minimum p-value test for H_0 under Poisson



Signal Identification: FDP and False Negatives

Negative binomial under H_a with $n = 40$ and $p = 10000$



Maize RNA-seq Study

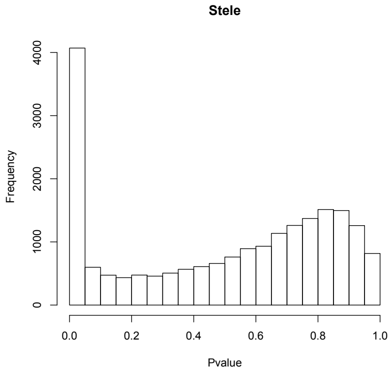
- NB model $\log(\mu_{i,j}) = \nu_j + X'_{g,i}\alpha_j + X'_{r,i}\beta_j + X'_{b,i}\gamma_j$
- α_j, β_j, γ_j: treatment effects for genotype, replication and barcoding
- Genotype effect:

$$\begin{aligned} &H_0 : \alpha_{1,j} = \alpha_{2,j} = \alpha_{3,j} = 0 \text{ for all } j \text{ vs.} \\ &H_a : \text{at least one component of } \alpha_j \text{ not equal to 0 for some } j. \end{aligned}$$

- The difference between the genotypes B73×Mo17 and Mo17×B73:

$$H_0 : \alpha_{2,j} = \alpha_{3,j} \text{ for all } j \text{ vs. } H_a : \alpha_{2,j} \neq \alpha_{3,j} \text{ for some } j.$$

Multi-Threshold Test for the Overall Genotype Effect



- Multi-Threshold Statistics

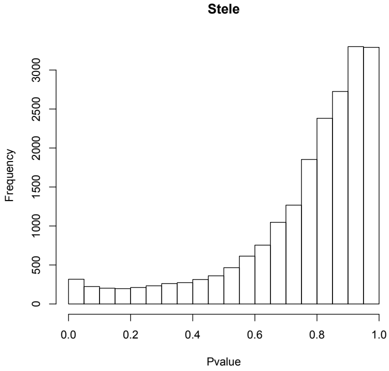
$$\mathcal{T}_n = 2826.1$$

- At 5% nominal level,

$$\text{Reject} \quad H_0 \quad \text{if} \quad \mathcal{T}_n > 3.09$$

- Strong evidence in favor of H_a
- Consistent with the findings from the P-value histogram

Multi-Threshold Test for Difference between MB and BM



- Multi-Threshold Statistics

$$\mathcal{T}_n = 22.5$$

- Reject H_0 since $\mathcal{T}_n > 3.09$
- Some genes DE between genotypes MB and BM
- Identify 32 DE genes

Conclusion

- Rare and faint signal detection for count data
- Multi-level thresholding test under GLM
- Step down procedure for signal identification
- Extension to GLMM

Reference

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