A network-based penalized regression method with application to genomic data

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Outline

- Problem
- Review: Existing penalized methods
- New method
  Pan, Xie and Shen (2010, *Biometrics*);
  Luo, Pan and Shen (2012, *Statistics in Biosciences*);
  Kim, Pan and Shen (2013, *Biometrics*);
- Numerical Results: simulated and real data
- Discussion

Introduction

- Problem: linear model

$$Y = \sum_{i=1}^{p} X_i \beta_i + \epsilon, \quad E(\epsilon) = 0, \tag{1}$$

  Feature: large p, small n.

- Q: variable selection; prediction
- Example 1: Li & Li (2008); Pan, Xie & Shen (2010) ...
  Y: clinical outcome, e.g. survival time;
  X_i: expression level of gene i.
- Example 2: eQTL analysis, Lan et al (2003, 2006); Pan (2009) ...
- Typical approaches: ignore any relationships among X_i's.
- In our applications: genes are related ...

e.g. as described *a priori* by

1) gene pathways/sets, e.g. KEGG, GO, etc (Ma et al 2007, 2010, ...; Wang et al 2009; Eng et al 2012; ...)

2) a gene network (here):

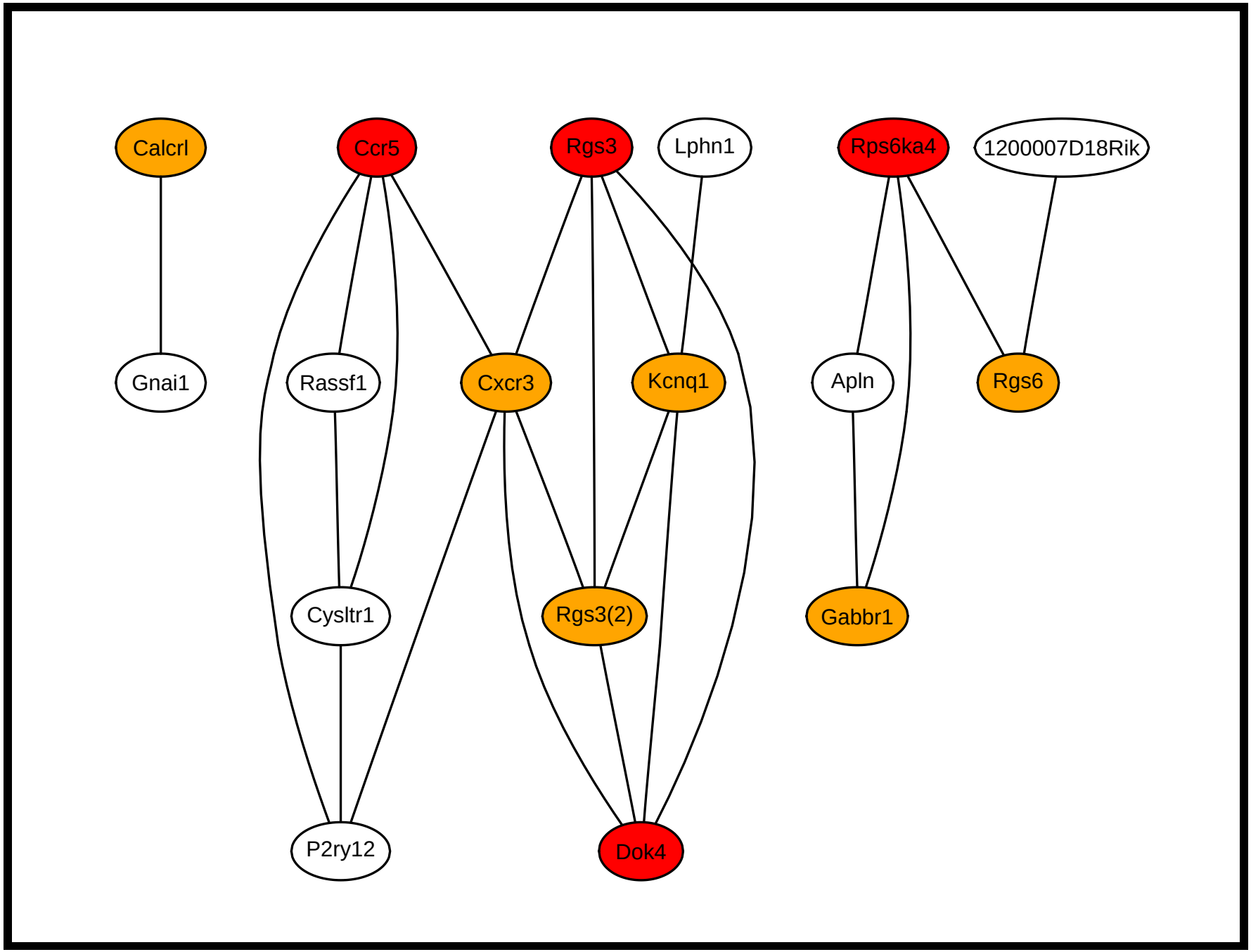

Calcrl
Ccr5
Rgs3
Lphn1
Rps6ka4
1200007D18Rik
Gnai1
Rassf1
Cxcr3
Kcnq1
Apln
Rgs6
Cysltr1
Rgs3(2)
Gabbr1
P2ry12
Dok4

Figure 1:

- Various types of gene networks: regulatory; co-expression; protein-protein interaction; pathways ...
- **Network assumption/prior 1**: if two genes $i \sim j$ in a network, then $|\beta_i| \approx |\beta_j|$, or $|\beta_i|/w_i \approx |\beta_j|/w_j$.
  Cluster/pathway-based analysis: force/prefer a common β_i or $|\beta_i|$ in a group (Park et al 2007; Eng et al 2012)/(Ma et al 2007; ...).
  Q: too strong?
- **Network assumption/prior 2**: if two genes $i \sim j$ in a network, then more likely to have $I(\beta_i \neq 0) = I(\beta_j \neq 0)$.
- Goal: utilize the network assumption/prior 2.
- How?

Review: Existing Methods

- Penalized methods: for "large p, small n"

$$\hat{\beta} = \arg\min_{\beta} L(\beta) + p_\lambda(\beta),$$

- Lasso (Tibshirani 1996):

$$p_\lambda(\beta) = \lambda \sum_{k=1}^{p} |\beta_k|.$$

  Feature: variable selection; some $\hat{\beta}_k = 0$.

- Elastic net (Zou and Hastie 2005)

$$p_\lambda(\beta) = \lambda \sum_{k=1}^{p} |\beta_k| + \lambda_2 \sum_{k=1}^{p} \beta_k^2.$$

  But ...

- A network-based penalty of Li and Li (2008): `Grace`

$$p_\lambda(\beta) = \lambda_1 \sum_{i=1}^{p} |\beta_i| + \lambda_2 \sum_{i \sim j} \left(\frac{\beta_i}{\sqrt{d_i}} - \frac{\beta_j}{\sqrt{d_j}} \right)^2, \qquad (2)$$

  d_i: degree of node i; two terms for diff purposes ...
  Related: Huang et al (2011); Ma et al (2012);
  Problem: if β_i and β_j have diff signs ...

- A modification by Li and Li (2010): `aGrace`

$$p_\lambda(\beta) = \lambda_1 \sum_{i=1}^{p} |\beta_i| + \lambda_2 \sum_{i \sim j} \left(\frac{\mathrm{sgn}(\tilde{\beta}_i)\beta_i}{\sqrt{d_i}} - \frac{\mathrm{sgn}(\tilde{\beta}_j)\beta_j}{\sqrt{d_j}} \right)^2, \qquad (3)$$

  $\tilde{\beta}_j$: an initial estimate based on Enet; a 2-step procedure.

- L_γ-norm with $\gamma > 1$ (Pan, Xie and Shen 2010):

$$p_\lambda(\beta; \gamma, w) = \lambda 2^{1/\gamma'} \sum_{i \sim j} \left(\frac{|\beta_i|^\gamma}{w_i} + \frac{|\beta_j|^\gamma}{w_j} \right)^{1/\gamma} \tag{4}$$

- w_i: smooth what?
  1) $w_i = d_i^{(\gamma+1)/2}$: smooth $|\beta_i|/\sqrt{d_i}$, as in Li and Li;
  2) $w_i = d_i$: smooth $|\beta_i|$
  Some theory under simplified cases.

- Feature: each term is an L_γ norm, $\gamma \geq 1$
  $\Longrightarrow$ **group** variable selection!; Yuan and Lin 2006, Zhao et al 2007.
  $\Longrightarrow$ tend to realize $\hat{\beta}_i = \hat{\beta}_j = 0$ if $i \sim j$!

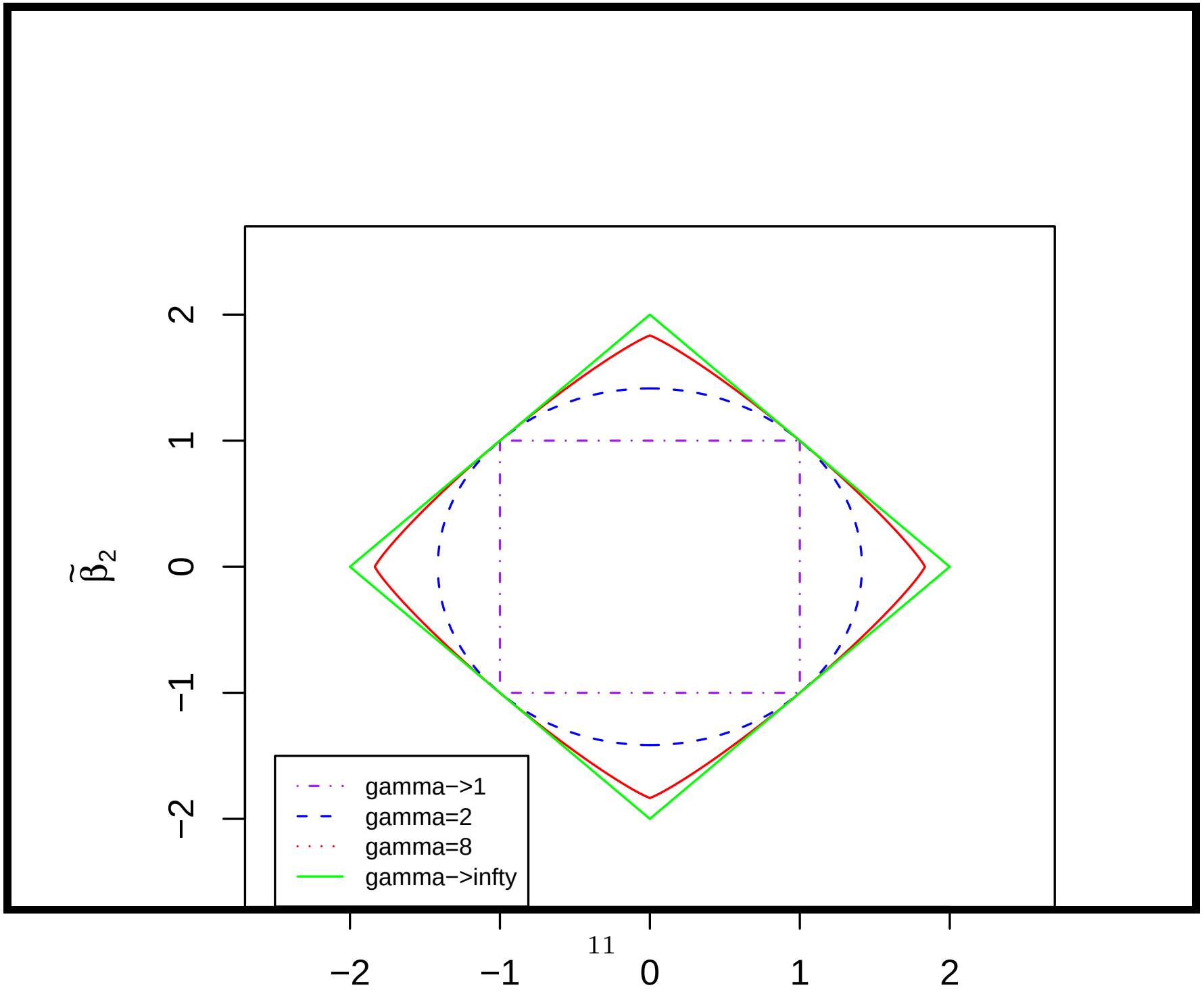
Corollary 1 *Assume that $X'X = I$. For any edge $i \sim j$, a sufficient condition for $\hat{\beta}_i = \hat{\beta}_j = 0$ is*

$$||(\tilde{\beta}_i, \tilde{\beta}_j)||_{\gamma'}^{(1/w_i, 1/w_j)} \leq \lambda 2^{1/\gamma'}, \tag{5}$$

and a necessary condition is

$$||(\tilde{\beta}_i, \tilde{\beta}_j)||_{\gamma'}^{(1/w_i, 1/w_j)} \leq \lambda 2^{1/\gamma'} + d_i + d_j - 2, \tag{6}$$

where $(\tilde{\beta}_i, \tilde{\beta}_j)$ are OLSEs.


gamma−>1
gamma=2
gamma=8
gamma−>infty
$\tilde{\beta}_2$
−2
−1
0
1
2

- γ: a larger γ smoothes more;
- L_∞: related to OSCAR (Bondell & Reich 2008)

$$p_\lambda = \lambda \sum_{i \sim j} \max \left(\frac{|\beta_i|}{\sqrt{d_i}}, \frac{|\beta_j|}{\sqrt{d_j}} \right)$$

  maximally forces $|\hat{\beta}_i|/\sqrt{d_i} = |\hat{\beta}_j|/\sqrt{d_i}$ if $i \sim j$!
- Other theoretical results (under simplified conditions): shrinkage effects, grouping effects ...
- Computational algorithm of Pan et al (2010): Generalized boosted lasso (GBL) (Zhao and Yu 2004); providing *approximate* solution paths.
- Use CV to choose tuning parameters, e.g. λ.
- Conclusion of Pan et al (2010): best for variable selection, but not necessarily in prediction (PMSE).

A surprise: $\gamma = \infty$ did not work well!

- Why?
- 1) Computational: convex programming of Luo et al (2012): Use Matlab CVX package; slower but better performance.
- 2) Bias due to group var selection:
  aL_∞: use a 2-step procedure as aGrace of Li and Li (2010).

New method

- Relax the smoothness assumption:
  New assumption: neighboring genes are more likely to participate or not participate at the same time; no assumption on the smoothness of regression coefficients.
- Prior: if $i \sim j$, more likely to have $I(\beta_i \neq 0) = I(\beta_j \neq 0)$ just for variable selection
- How to approximate the discontinuous $I(\beta_j \neq 0)$?
  Truncated Lasso Penalty (Shen, Pan & Zhu 2012, *JASA*):

$$J_\tau(\beta_j) = \min(1, |\beta_j|/\tau) \to I(\beta_j \neq 0)$$

  as $\tau \to 0^+$; see Fig:

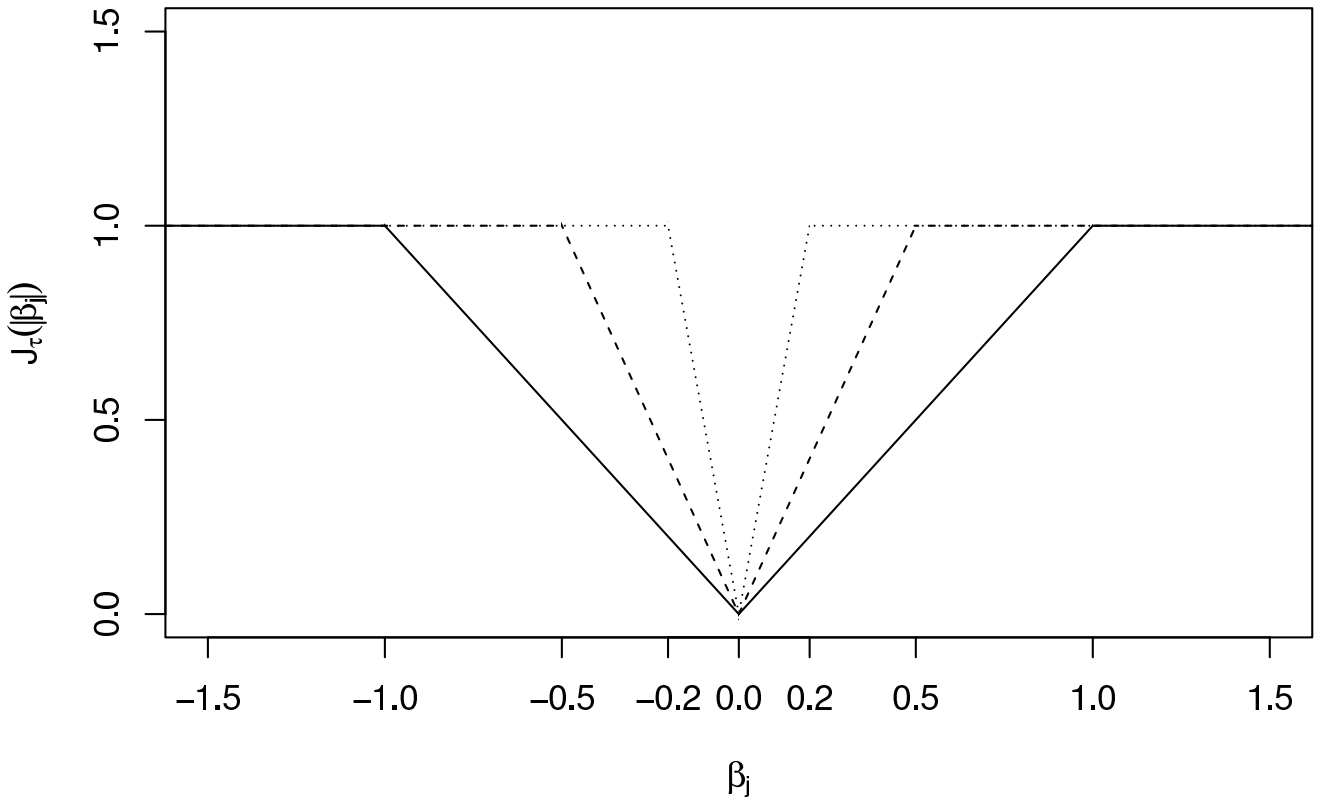


Figure 3:

- TLP: related to SCAD (Fan and Li 2001), MCP (Zhang 2010), SELO (Dicker et al 2012; Li, Wang & Lin 2012), ..., but ...

- Use a new penalty to approximate $\sum_{i\sim j} |I(\beta_i \neq 0) - I(\beta_j \neq 0)|$:

$$p_\lambda(\beta;\tau) = \lambda \sum_{i\sim j} |J_\tau(\beta_i) - J_\tau(\beta_j)|.$$

- But $p_\lambda(\beta;\tau)$ is not convex; use difference convex (DC) programming (Tao & An 1998)!
  related to MM (Hunter & Lange 2010).

- Two tricks:
  1) $J_\tau(z) = \frac{1}{\tau}(|z| - \max(|z| - \tau, 0))$;
  2) $|u - v| = 2\max(u, v) - (u + v)$.

- $TTLP_I$:

$$p(\beta) = \lambda_1 \sum_{j=1}^{p} J_\tau(|\beta_j|) + \lambda_2 \sum_{j\sim j'} \left| J_\tau\left(\frac{|\beta_j|}{w_j}\right) - J_\tau\left(\frac{|\beta_{j'}|}{w_{j'}}\right) \right|, \quad (7)$$

- $LTLP_I$:

$$p(\beta) = \lambda_1 \sum_{j=1}^{p} |\beta_j| + \lambda_2 \sum_{j \sim j'} \left| J_\tau \left(\frac{|\beta_j|}{w_j} \right) - J_\tau \left(\frac{|\beta_{j'}|}{w_{j'}} \right) \right|, \qquad (8)$$

- $LTLP_I$:

$$p(\beta) = p_1(\beta) - p_2(\beta),$$

$$p_1(\beta) = \frac{1}{\tau} \left(\lambda_1 \sum_{j=1}^{p} |\beta_j| + \lambda_2 \sum_{j' \sim j} 2\max(u_j, v_j) \right),$$

$$p_2(\beta) = \frac{1}{\tau} \left(\lambda_2 \sum_{j' \sim j} (u_j + v_j) \right),$$

$u_j = \frac{|\beta_j|}{w_j} + \max(\frac{|\beta_{j'}|}{w_{j'}} - \tau, 0)$ and $v_j = \frac{|\beta_{j'}|}{w_{j'}} + \max(\frac{|\beta_j|}{w_j} - \tau, 0)$.

- Linearizing p_2 at a current estimate $\hat{\beta}^{(m-1)}$ and ignoring terms

independent of β, we obtain a convex approximation of $S(\beta)$:

$$\begin{aligned} S^{(m)}(\beta) &= \frac{1}{2}\|Y - X\beta\|^2 + \frac{\lambda_1}{\tau}\sum_{j=1}^{p}|\beta_j| + \frac{\lambda_2}{\tau}\sum_{j\sim j'} 2\max(u_j, v_j) \\ &\quad -\frac{\lambda_2}{\tau}\sum_{j\sim j'}\left(\frac{\beta_j}{w_j}\mathrm{Sgn}(\hat{\beta_j}^{(m-1)})[1 + I(\frac{|\hat{\beta}_j^{(m-1)}|}{w_j} > \tau)]\right. \\ &\quad \left. + \frac{\beta_{j'}}{w_{j'}}\mathrm{Sgn}(\hat{\beta_{j'}}^{(m-1)})[1 + I(\frac{|\hat{\beta_{j'}}^{(m-1)}|}{w_{j'}} > \tau)]\right), \end{aligned}$$

which is minimized to obtain an updated estimate $\hat{\beta}^{(m)}$.

- Since $S^{(m)}(\beta)$ is convex, we use Matlab package `CVX`.
- **Theorem**: the above DC algorithm monotonically converges to a local minimum in finite steps.
- Use grid search and CV to determine the choice of $(\tau, \lambda_1, \lambda_2)$.

- Simulation set-ups:
  network: 10 subnetworks, each with one TF connects to ist 10 targets (Li and Li 2008);
  $n = 50$, $p = p_1 + p_0 = 44 + 66$;

- True β: for $j \sim j'$,
  Set-up 1: $\beta_j/\sqrt{d_j} = \beta_{j'}/\sqrt{d_{j'}}$;
  Set-up 2: $|\beta_j|/\sqrt{d_j} = |\beta_{j'}|/\sqrt{d_{j'}}$;
  Set-up 3: $|\beta_j|/\sqrt{d_j} \neq |\beta_{j'}|/\sqrt{d_{j'}}$ but $I(\beta_j \neq 0) = I(\beta_{j'} \neq 0)$.

- Use $w_j = \sqrt{d_j}$ (and $w_j = 1$, not shown).

- $ME = (\beta - \hat{\beta})' E(X'X)(\beta - \hat{\beta})$;
  PE: prediction mean squared error for Y; PE=ME+c;
  $TP = |\{j : \beta_j \neq 0, \hat{\beta}_j \neq 0\}|$; (max TP=22)
  $FP = |\{j : \beta_j = 0, \hat{\beta}_j \neq 0\}|$;

Set-up 1: mean[median](sd)

Method	ME(sd)	PE(sd)	TP	FP
Lasso	44.2(13.2)	66.2(13.1)	13.5[14](3.2)	16.8[13](19.2)
Enet	34.2(13.1)	65.0(13.5)	16.5[17](3.7)	22.2[18](16.6)
Grace	4.7(3.6)	39.7(5.8)	22.0[22](0.1)	59.5[63](21.2)
aGrace	23.9(16.4)	55.6(14.4)	17.6[18](4.1)	29.4[23.5](22.3)
L_∞	14.2(8.0)	50.4(11.2)	22.0[22](0.0)	9.7[8](6.8)
aL_∞	4.3(4.1)	38.8(6.0)	22.0[22](0.0)	4.1[2](5.4)
$TTLP_I$	12.4(12.0)	45.4(9.1)	21.5[22](2.7)	20.2[1](28.3)
$LTLP_I$	9.6(8.5)	43.4(8.5)	21.7[22](1.4)	23.4[22](17.0)

Set-up 2: mean[median](sd)

Method	ME(sd)	PE(sd)	TP	FP
Lasso	34.6(8.8)	67.9(11.4)	10.2[9.5](3.0)	13.4[9.0](15.4)
Enet	34.8(8.5)	68.2(11.4)	13.2[13.0](4.3)	24.4[18](22.1)
Grace	27.1(5.7)	59.8(9.0)	18.5[19](3.4)	45.1[43.5](25.1)
aGrace	25.3(10.9)	58.4(11.6)	17.5[19](5.0)	41.9[39.5](24.1)
L_∞	34.5(10.2)	65.1(12.2)	20.9[22](2.6)	15.2[13](11.0)
aL_∞	20.7(9.9)	53.5(11.6)	20.7[22](3.1)	8.3[5](10.7)
$TTLP_I$	28.5(11.0)	59.5(11.3)	21.0[22](3.3)	26.7[15](28.6)
$LTLP_I$	23.2(8.1)	55.3(9.3)	21.4[22](2.2)	37.2[33](21.4)

Set-up 3: mean[median](sd)

Method	ME(sd)	PE(sd)	TP	FP
Lasso	36.2(9.4)	67.0(11.3)	10.0[10](3.3)	13.6[10](16.3)
Enet	34.9(7.9)	65.8(10.3)	12.7[12](3.8)	22.7[17](19.2)
Grace	34.9(7.8)	65.4(10.6)	13.6[14](4.2)	24.8[19](19.3)
aGrace	36.2(8.4)	63.1(9.0)	15.2[15](5.6)	32.0[24](24.3)
L_∞	33.9(8.1)	65.1(10.3)	15.3[15](4.6)	13.8[11](11.5)
aL_∞	37.6(9.2)	66.0(12.1)	15.0[15](4.7)	9.7[7.5](11.0)
$TTLP_I$	34.2(10.1)	63.9(10.9)	19.1[22](5.2)	20.1[13](22.7)
$LTLP_I$	31.3(7.4)	61.1(9.6)	20.5[22](3.7)	39.2[44](21.9)

Example

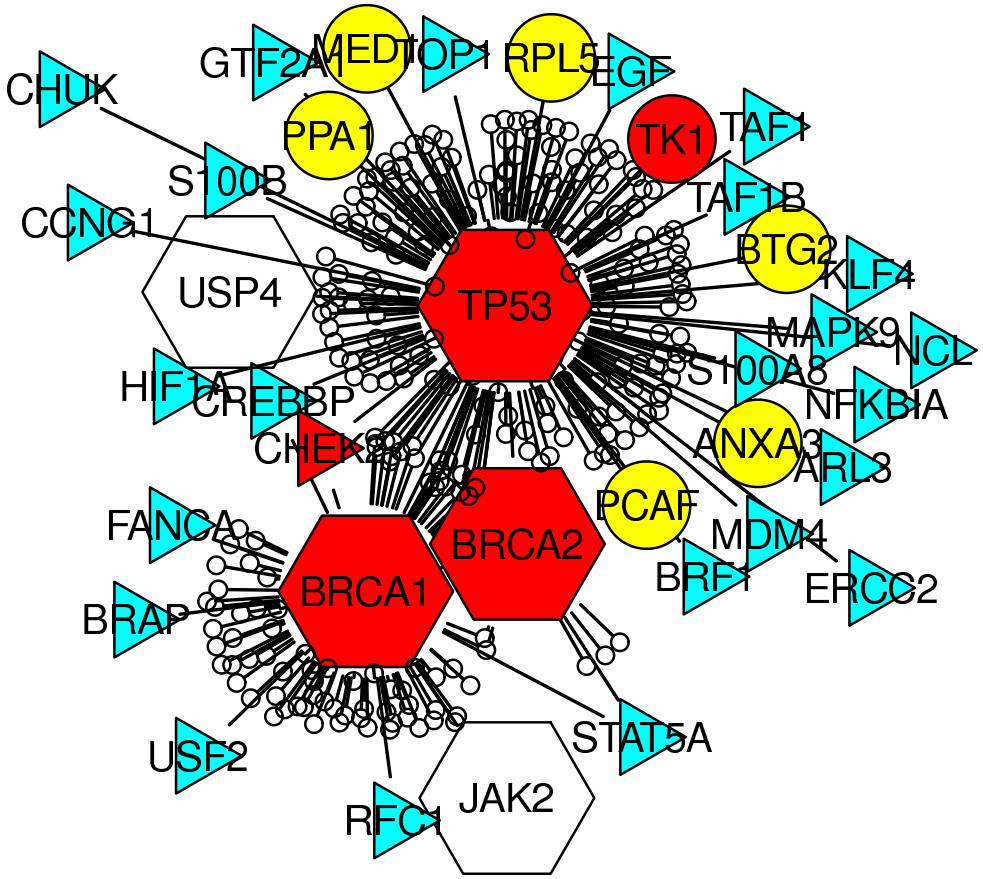
- $n = 286$ breast cancer patients (Wang et al 2005);
  (time to) metastasis within a 5-year follow-up after surgery;
  106 events;
- $n = 295$ breast cancer patients (van de Vijver et al 2002);
  (time to) metastasis within a 5-year follow-up after surgery;
  78 events;
- Consider three tumor suppressor genes, $BRCA1$,
  $BRCA2, TP53$, and their direct neighbors in a PPI network
  (Chuang et al 2007);
- Fit a linear model
  Y: binary; X: expression levels of $p = 294$ genes;
- Goal: variable selection
  Q: which genes' expression levels predict the survival time?

- Among $p = 294$ genes, 18 cancer (CA) genes.
- Split the sample into $n = 95$, 95, 96 for training, tuning, testing;
  repeat 20 times.

Method	PE	# CA	# Genes
Lasso	0.235(0.004)	0.30[0.00](0.13)	8.80[8.00](1.91)
Final	-	1	30
Enet	0.227(0.003)	0.20[0.00](0.09)	9.90[1.00](2.60)
Final	-	2	51
Grace	0.227(0.003)	0.70[1.00](0.16)	9.50[2.50](2.38)
Final	-	2	49
aGrace	0.229(0.003)	1.30[1.00](0.25)	10.20[6.00](2.10)
Final	-	2	52
L_{inf}	0.236(0.005)	0.10[0.00](0.07)	10.35[7.50](1.97)
Final	-	0	3
aL_{inf}	0.239(0.005)	0.10[0.00](0.07)	10.20[7.50](2.43)
Final	-	0	3
TTLP	0.282(0.015)	2.90[3.00](0.34)	12.00[8.00](2.68)
Final	-	4	30
LTLP	0.256(0.009)	1.35[1.50](0.28)	11.10[8.00](2.07)
Final	-	4	30

	# Freq of selecting BRCA1, BRCA2 and TP53
Lasso	BRCA1 (1), BRCA2 (0), TP53 (1)
Enet	BRCA1 (0), BRCA2 (0), TP53 (0)
Grace	BRCA1 (7), BRCA2 (2), TP53 (2)
aGrace	BRCA1 (10), BRCA2 (4), TP53 (9)
L_∞	BRCA1 (0), BRCA2 (0), TP53 (0)
aL_∞	BRCA1 (0), BRCA2 (0), TP53 (0)
$TTLP_I$	BRCA1 (20), BRCA2 (10), TP53 (20)
$LTLP_I$	BRCA1 (9), BRCA2 (5), TP53 (9)

Figure 4: The final models by $TTLP_I$. 5 genes in hexagons: in both models; triangles/big circles: in only one; 5 red ones: BC genes.



Discussion

- Bayesian approaches (Moni and Li 2009; Li and Zhang 2009; Tai, Pan & Shen 2010):
  prior prob's $Pr(\beta_i \neq 0)$ modeled by a network-induced MRF.
- A new penalty (Zhu, Shen & Pan 2013, JASA):

$$p_\lambda(\beta;\tau) = \lambda \sum_{i\sim j} \left[J_\tau(\beta_i + \beta_j) + J_\tau(\beta_i - \beta_j) \right],$$

  aiming for

$$\sum_{i\sim j} \left| |\beta_i| - |\beta_j| \right|.$$

- Another application: eQTL mapping (Pan 2009)

$$Y_g = X\beta_g + \epsilon_g, \;\; E(\epsilon_g) = 0, \tag{9}$$

  for $g = 1, ..., G$.
  X: DNA markers; obs $(Y_1, ..., Y_G, X)$.

Q: which markers are associated with Y_g?
$\Longrightarrow$ variable selection or ...

- Typical approaches:
  Gene-by-gene, separately, with possible var selection (Broman and Speed 2002; Wang et al 2011; ...)
- BUT, genes are related...
  e.g. as described by pathways or clusters (Lan et al 2003; Chun and Keles 2009; Zhang et al 2010; ...)
  or by a co-expression network (Pan 2009).
  $\Longrightarrow Y_g's$ are correlated, and more likey to be co-regulated!
- Network assumption/prior: if two genes $g \sim h$ in a network, then $|\beta_g| \approx |\beta_h|$, or, $I(\beta_g \neq 0) = I(\beta_h \neq 0)$.
- Goal: utilize the above assumption/prior.
- How?

- Reformulate the orginal multiple regressions to a single regression:
  $Y_c = (Y_1', ..., Y_G')'$,
  $X_c = diag(X, ..., X)$,
  $\beta = (\beta_1', ..., \beta_G')'$,

$$Y = X\beta + \epsilon, \;\; E(\epsilon) = 0, \tag{10}$$

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Thank you!