A novel and efficient algorithm for de novo discovery of mutated driver pathways in cancer

Binghui Liu, Chong Wu, Xiaotong Shen, Wei Pan

University of Minnesota, Minneapolis, MN 55455

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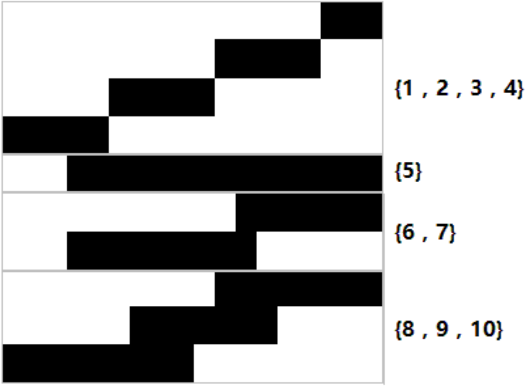
Introduction

- Given: an $n \times p$ mutation matrix $\mathbf{A}$ with entry $A_{ij} = 1$ if gene j is mutated in patient i, and $A_{ij} = 0$ otherwise.
- Goal: to identify a subset B of genes as **driver** gene.
- Vandin et al (2012, *Genome Res*) proposed two criteria:
    - Coverage: many patients with mutations in B, maximize $|\Gamma(B)|$ with $\Gamma(B) = \bigcup_{j \in B} \Gamma(j)$ and $\Gamma(j) = \{i : A_{ij} = 1\}$.
    - Exclusitivity: mutations in B do not occur simultaneously on any patient, minimize $\omega(B) = \sum_{j \in B} |\Gamma(j)| - |\Gamma(B)|$.
- Overall, minimize

$$f(B) = \frac{\omega(B)}{n} - \frac{|\Gamma(B)|}{n} = \frac{1}{n} \sum_{j \in B} |\Gamma(j)| - \frac{2}{n} |\Gamma(B)|. \qquad (1)$$

- Challenge: a combinatorial (i.e. NP-hard) problem!
  not feasible to have an exact solution.
  use approximate solutions, e.g. Monte Carlo methods...



B_0	$f(B_0)$
{1,2,3,4}	−1.00
{5}	−0.85
{6,7}	−0.80
{8,9,10}	−0.70

A toy example, where each column represents a patient, each row represents a gene and each black entry represents the mutation.

Existing approaches

- Dendrix-MCMC: Vandin et al (2012, *Genome Res*);
- Multi-dendrix-MCMC: Leiserson et al (2013, *PLOS Comp Biol*);
- Binary linear programming (BLP) and genetic algorithm (GA): Zhao et al (2012, *Bioinformatics*);

New formulation

- Define: $B = B(\boldsymbol{\beta}) = \{j \in V : |\beta_j| \neq 0\}$.
- Rewrite (1) as

$$f(B(\boldsymbol{\beta})) = \frac{1}{n}\sum_{j=1}^{p} I(|\beta_j| \neq 0)A_{\cdot,j} - \frac{2}{n}\sum_{i=1}^{n} I\Big(\sum_{j=1}^{p} A_{ij} I(|\beta_j| \neq 0) \neq 0\Big). \quad ($$

- Challenge: discontinuous indicator function $I(\beta_j \neq 0)$.
- Our solution: use a TLP to approximate $I(.)$:

$$\min(|\beta_j|/\tau_1, 1) \to I(|\beta_j| \neq 0) \qquad \text{as } \tau_1 \to 0^+.$$

- Note: TLP as a non-convex penalty better than the popular Lasso in regularization, e.g. regression/classification, Gaussian graphical models (GGMs) (Shen et al 2012, *JASA*); fusion: network-based regression (Kim et al 2013, *Biometrics*; Zhu et al 2013, *JASA*), multiple GGMs (Gao et al 2016, *EJS*), ...

$$\tau_1 \min(|\beta_j|/\tau_1, 1) = \min(|\beta_j|, \tau_1).$$

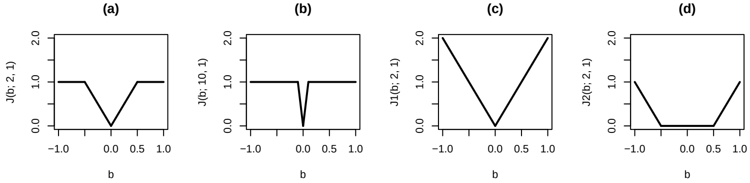


Figure: TLP $J_T(b;\tau)$ (a) with $\tau = 0.5$, or (b) with $\tau = 0.1$; J_T in (a) is decomposed into a difference of two convex functions J_1 in (c) and J_2 in (d).

Computation: DC algorithm

- New target:

$$\begin{aligned} S(\boldsymbol{\beta}) &= \frac{1}{n}\sum_{j=1}^{p}\min\left(\beta_j/\tau_1,1\right)A_{\cdot,j} - \frac{2}{n}\sum_{i=1}^{n}\min\left(\sum_{j=1}^{p}A_{ij}\beta_j/\tau_1,1\right) \\ &\quad +\lambda\sum_{j=1}^{p}\min\left(\beta_j/\tau_2,1\right)+\frac{\alpha}{n}\sum_{j=1}^{p}\beta_j^2, \qquad (3) \end{aligned}$$

  with respect to $\boldsymbol{\beta}=(\beta_1,...,\beta_p)'\in[0,+\infty)^p$.

- Note: The TLP and the ridge penalty ensure sparse and proper solutions.
- DC decomposition of TLP:

$$\min(\frac{|z|}{\tau},1)=\frac{|z|}{\tau}-\max\left(\frac{|z|}{\tau}-1,0\right).$$

- At iteration m with the current estimate,

$$
\begin{aligned}
S^{(m)}(\boldsymbol{\beta}) = \quad & \boldsymbol{\beta}' \left(\mathrm{diag}(\mathbf{A}_{\cdot}) I(\hat{\boldsymbol{\beta}}^{(m-1)} \leq \tau_1)/n\tau_1 + \lambda I(\hat{\boldsymbol{\beta}}^{(m-1)} \leq \tau_2)/\tau_2 - 2\mathbf{A}_{\cdot}/n\tau_1 \right) + \\
& \frac{2}{n} \sum_{i=1}^{n} \max\Big(\sum_{j=1}^{p} A_{ij}\beta_j/\tau_1 - 1, 0\Big) + \frac{\alpha}{n}\boldsymbol{\beta}'\boldsymbol{\beta}, \qquad (4)
\end{aligned}
$$

- $S^{(m)}(\boldsymbol{\beta})$ is convex; can apply Matlab CVX or subgradient descent.
- Theorem: The above DC algorithm converges to a local minimizer montonically in finite steps.
- Tuning parameter selection: $\alpha = 0.001$, $\tau_1 = 1$; others by CV.

Table: Applied to the mutation data of glioblastoma multiforme (TCGA 2008),the new method MCSS identified multiple sets of low-cost mutated genes, grouped in terms of associated pathways.

Pathway	Core mutations	$\hat{B}$	$f(\hat{B})$
p53 signalling	*CDKN2A, MDM2, MDM4, TP53*	(*CDKN2A, MDM2, MDM4, TP53*)	-55
		(*CDKN2A, DTX3, TP53*)	-57
		(*CDKN2A, TP53*)	-53
		(*CDKN2B, TP53*)	-53
RB signalling	*CDKN2A/B, CDK4, RB1*	(*CDKN2B, CYP27B1, RB1*)	-62
		(*CDKN2B, ERBB2, RB1, TSPAN31*)	-64
		(*CDKN2A, CYP27B1, RB1*)	-56
		(*CDKN2B, CYP27B1, NF1*)	-56
		(*CDKN2A, CYP27B1, NF1*)	-54
		(*CDKN2B, CYP27B1*)	-54
RAS signalling	*EGFR, NF1*	(*EGFR, KDR, NF1*)	-52
		(*MTAP, TP53, TSFM*)	-56
		(*CYP27B1, MTAP, PTEN*)	-55
		(*CDK4, MTAP, PTEN*)	-55
		(*EGFR, TP53*)	-52

i

Table: Results in Simulation I based on 100 simulation replications with $(p_1, p_2, p_3) = (0.95, 0.01, 0.05)$. The sample means (SD in parentheses) of correct (C) or incorrect (IC) numbers of non-zero estimates, average differences of the cost (ADC) between the true gene subset $B_0 = \{1, 2, 3, 4\}$ and the estimated subset $\hat{B}$, that is, $\frac{f(B_0)-f(\hat{B})}{n}$, and the running time (RT) (in minutes) of the algorithms.

n	p	Method	C	IC	ADC	$\hat{c}_1$ $[c_1]$	$\hat{c}_2$ $[c_2]$	R
50	1000	MCSS	4 (0)	0 (0)	0 (0)	.95 [.95]	.01 [.00]	.22 (
		Dendrix	3.80 (.41)	.50 (.94)	-.02 (.04)	.94 [.95]	.01 [.00]	16.89 (
		Mdendrix	3.90 (.30)	.15 (.36)	-.01 (.03)	.95 [.95]	.01 [.00]	.81 (
		BLP	3.39 (.86)	3.82 (2.59)	.05 (.03)	.99 [.95]	.00 [.00]	.01 (
		GA	3.90 (.38)	2.13 (1.69)	.04 (.03)	.98 [.95]	.01 [.00]	2.97 (
50	10000	MCSS	4 (0)	0 (0)	0 (0)	.95 [.95]	.01 [.01]	1.67 (
		Dendrix	1.25 (1.02)	5.96 (3.62)	-.24 (.04)	.83 [.95]	.02 [.01]	67.06 (
		Mdendrix	1.45 (1.23)	5.25 (4.02)	-.24 (.03)	.83 [.95]	.03 [.00]	1.88 (
		BLP	3.42 (.91)	2.72 (2.06)	.05 (.03)	.99 [.95]	.01 [.00]	.27 (
		GA	3.93 (.25)	1.50 (.92)	.04 (.02)	.98 [.95]	.01 [.00]	284.92 (

Discussion

- A general method to approximate the indicator function; more applications (and modifications) may be worthwhile.
- Considered integrative analysis of mutation and gene expression data.
  improved performance with GE data;
  non-linear; binary linear programming (BLP) not applicable.
- TLP is a general non-convex penalty applied to many high-dimensional problems.
  can be regarded as a refined version of Lasso; TLP=Lasso with larger τ;
  better empirical and theoretical performance;
  computationally more demanding (with an extra tuning parameter τ).

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- **Thank you!**