Generalized Group Elastic Net for Predictive Biomarker Identification

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Predictive biomarker identification is a significant problem when targeting patient subpopulation who gets an enhanced benefit under treatment. This paper proposed a new method, Predictive Effects Net (PEN), based on group lasso and special hierarchical structure for figuring out predictive effects. The new approach takes predictive biomarkers as interaction effects between treatment and biomarker. To show PEN has an supreme performance, this paper shows simulations in different scenerios and comparisons with several other variable selection methods.

Introduction

Prognostic biomarkers and predictive biomarkers.

Why decision trees is not workable? Because the sample size in real clinical datasets is too small, typically no more than 100 patients.

Group lasso (*1*)

Elastic net (*2*) adaptive weights for elastic net (*3*)

Hierarchical Group lasso for interactions (*4*)

Overlapping group lasso (*5*) (*6*) (*7*)

Sparse Group Lasso (*8*) (*9*)

Structured group lasso (*10*) Group lasso for logistic regression (*11*)

Other variable selection methods:

GUIDE: a regression tree (*12*) (*13*)

SIS: screening (*14*) (*15*)

SIR: (*16*) (*17*)

Stepwise selection: (*18*)

Methods

Model

$$Y = X_0\beta_0 + X_T\beta_\tau + X_1\beta_1 + X_T \otimes X_1\beta_2 + \epsilon$$

Where X_0 is the baseline variables, X_T is the treatment variable, X_1 is the high dimensional design matrix of genes, i.e. gene expression levels, SNP and mutations, and $X_T \otimes X_1$ is the interaction between genes and treatment. $\beta = (\beta_0, \beta_\tau, \beta_1, \beta_2)$ is the corresponding coefficients. ϵ is random error.

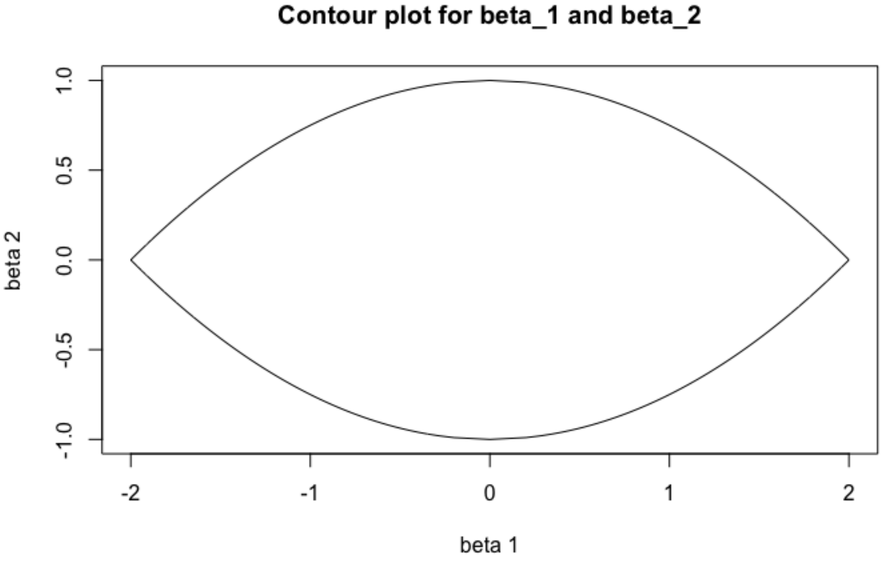
Let

$$X = [X_0, X_T, X_1^{(1)}, \ldots, X_m^{(1)}, X_T X_1^{(1)}, \ldots, X_T X_1^{(m)}]$$

and

$$\beta = [\beta_0, \beta_\tau, \beta_1^{(1)}, \ldots, \beta_1^{(m)}, \beta_2^{(1)}, \ldots, \beta_2^{(m)}]$$

For each gene l, its prognostic and predictive design matrix is denoted as $X^{(l)} = [X_1^{(l)}, X_T X_1^{(l)}]$ and its corresponding coefficients are $\beta^{(l)} = [\beta_1^{(l)}, \beta_2^{(l)}]$



Loss Function

We used group lasso and elastic net for variables selection when $n \ll p$, and assumed the hierarchical relationship between prognostic biomarkers and predictive biomarkers, that is the predictive biomarkers should be a prognostic biomarkers. The loss function is

$$\min_{\theta} f(\beta|Y, X_0, X_T, X_1) + g(\beta)$$

$$g(\beta) = \lambda_1 \sum_i \phi_i |\beta_2^{(i)}| + \lambda_1 \sum_i \psi_i \sqrt{(\beta_1^{(1)})^2 + (\beta_2^{(1)})^2} + \lambda_2(\| \beta_1 \|_2^2 + \| \beta_2 \|_2^2)$$

Where $\beta = (\beta_0, \beta_\tau, \beta_1, \beta_2)$ is the parameter, and $f(\beta|Y, X_0, X_T, X_1)$ is L-2 loss function. When the model is the ordinary linear model, the L-2 loss function is $\| Y - (X_0\beta_0 + X_T\beta_\tau + X_1\beta_1 + X_T \otimes X_1\beta_2) \|^2$. Penalty function $g(\beta)$ can construct a complex hierarchical selection of β_1 and β_2, that nonzero β_2 is a sufficient but not necessary condition for nonzero β_1. The contour plot for a pair of β_1 and β_2 is shown in Figure 1. λ_1 and λ_2 are regularization parameters.

Criterion and Adaptive Weights

KKT conditions

KKT (*19*)

For group $\hat{\beta^{(l)}}$, the KKT condition is

$$X^{(l)^T}(Y - X\hat{\beta}) = \lambda_1\phi_l \begin{bmatrix}0\\ v\end{bmatrix} + \lambda_1\psi_l u + \frac{1}{2}\lambda_2\hat{\beta}^{(l)} \tag{1}$$

where

$$v = \begin{cases}\text{sign}(\hat{\beta}_2^{(l)}) & \text{if } \hat{\beta_2}^{(l)} \neq 0\\ \in \{v : |v|_1 \leq 1\} & \text{if } \hat{\beta_2}^{(l)} = 0\end{cases} \tag{2}$$

$$u = \begin{cases}\hat{\beta}^{(l)}/ \parallel \hat{\beta}^{(l)} \parallel_2 & \text{if } \hat{\beta}^{(l)} \neq 0\\ \in \{u :\parallel u \parallel_2 \leq 1\} & \text{if } \hat{\beta}^{(l)} = 0\end{cases} \tag{3}$$

- $\hat{\beta}^{(l)} = 0$ if

  $$S(X_1^{(l)^T} r_{(-l)}, 0)^2 + S(X_2^{(l)^T} r_{(-l)}, \lambda_1\phi_l)^2 \leq \lambda_1^2\psi_l^2 \tag{4}$$

  where

  $$S(z, a) = \text{sign}(z)(|z| - a)_+ \tag{5}$$

  and

  $$r_{(-l)} = Y - X^{(-l)^T}\hat{\beta}^{(-l)} \tag{6}$$

We can find

$$u = \begin{bmatrix} \frac{X_1^{(l)} r_{(-l)}}{\lambda_1 \psi_l} \\ \frac{S({X_2^{(l)}}^T r_{(-l)}, \lambda_1 \phi_l)}{\lambda_1 \psi_l} \end{bmatrix} \tag{7}$$

$$v = \begin{bmatrix} 0 \\ \frac{{X^{(l)}}^T r_{(-l)} - S({X_2^{(-l)}}^T r_{(-l)}, \lambda_1 \phi_l)}{\lambda_1 \psi_l} \end{bmatrix} \tag{8}$$

Thus, we have $\parallel u \parallel_2 \leq 1$ and $|v|_\infty \leq 1$, so that subgradient equation 1 was satisfied with $\hat{\beta}^{(l)} = 0$

- if $\hat{\beta}^{(l)} \neq 0$ but $\hat{\beta}_2^{(l)} = 0$, we need to satisfy

  $${X^{(l)}}^T (Y - {X^{(-I(l))}}^T \hat{\beta}^{(-I(l))}) = \lambda_1 \phi_l \begin{bmatrix} 0 \\ v \end{bmatrix} + \lambda_1 \psi_l \frac{\hat{\beta}^{(l)}}{\parallel \hat{\beta}^{(l)} \parallel_2} + \frac{1}{2} \lambda_2 \hat{\beta}^{(l)} \tag{9}$$

  we have $\hat{\beta}_2^{(l)} = 0$ if

  $${X_2^{(l)}}^T r_{(-I(l))} \leq \lambda_1 \phi_l \tag{10}$$

  and $r_{(-I(l))} = Y - {X^{(-I(l))}}^T \hat{\beta}^{(-I(l))}$ and $I(l)$ is the interaction effect nested in biomarker lth group.

- $\hat{\beta}^{(l)} \neq 0$ as well as $\hat{\beta}_2^{(l)} \neq 0$, we have

  $${X^{(l)}}^T (Y - {X^{(-I(l))}}^T \hat{\beta}^{(-I(l))}) = \lambda_1 \phi_l \begin{bmatrix} 0 \\ \text{sign}(\hat{\beta}_2^{(l)}) \end{bmatrix} + \lambda_1 \psi_l \frac{\hat{\beta}^{(l)}}{\parallel \hat{\beta}^{(l)} \parallel_2} + \frac{1}{2} \lambda_2 \hat{\beta}^{(l)} \tag{11}$$

  Then we get

  $$\begin{aligned} \hat{\beta}_2^{(l)} &= \frac{{X_2^{(l)}}^T (Y - X^T \hat{\beta}^{(-I(l))}) - \lambda_1 \phi_l \text{sign}(\hat{\beta}_2^{(l)})}{{X_2^{(l)}}^T X_2^{(l)} + \frac{\lambda_1 \psi_l}{\|\hat{\beta}^{(l)}\|_2} + \frac{1}{2} \lambda_2} \\ &= \frac{S({X_2^{(l)}}^T r_{(-I(l))}, \lambda_1 \phi_l)}{{X_2^{(l)}}^T X_2^{(l)} + \frac{\lambda_1 \psi_l}{\|\hat{\beta}^{(l)}\|_2} + \frac{1}{2} \lambda_2} \end{aligned} \tag{12}$$

$$\hat{\beta}_1^{(l)} = \frac{{X_2^{(l)}}^T r_{(-G(l))}}{{X_1^{(l)}}^T X_1^{(l)} + \frac{\lambda_1 \psi_l}{\|\hat{\beta}^{(l)}\|_2} + \frac{1}{2}\lambda_2} \tag{13}$$

$$\hat{\beta}_0 = \frac{X_0^T r_{(-0)}}{X_0^T X_0} \tag{14}$$

$$\hat{\beta}_\tau = \frac{X_T^T r_{(-T)}}{X_T^T X_T} \tag{15}$$

Adaptive Weights

To give each biomarker equal probability to be prognostic and predictive, we define adaptive weights via a null model that the residual $\epsilon = r_{(-I(l))}$ is a normal random error where $\epsilon \sim N(0, \sigma^2)$ when $\beta_2^{(l)} = 0$. Let

$$\begin{aligned} \| {X_2^{(l)}}^T r_{(-I(l))} \|_2 &= \lambda_1 \phi_l \\ E[({X_2^{(l)}}^T r_{(-I(l))})^2] &= \lambda_1^2 \phi_l^2 \end{aligned} \tag{16}$$

Thus, we can get $\lambda_1^2 \phi_l^2 = \text{Var}({X_2^{(l)}}^T r_{(-I(l))})$ and

$$\phi_l \propto \| X_2^{(l)} \|_2 \tag{17}$$

Since λ_1 is regularization parameter, we define $\phi_l = \| X_2^{(l)} \|_2$ without loss generality.

On the other hand, based on inequality 4 and results from formula 16, we let

$$\mathbb{E}[S({X_1^{(l)}}^T r_{(-l)}, 0)^2 + S({X_2^{(l)}}^T r_{(-l)}, \lambda_1 \phi_l)^2] = \lambda_1^2 \psi_l^2 \tag{18}$$

and assume $r_{(-l)} = \epsilon \sim N(0, \sigma^2)$ if $\beta^{(l)} = 0$, thus $\epsilon_1 = {X_2^{(l)}}^T r_{(-l)} \sim N(0, \lambda_1^2\phi_l^2)$ and $\epsilon_0 = \epsilon_1/\lambda_1\phi_l \sim N(0,1)$.

$$\begin{aligned}\mathbb{E}[S({X_2^{(l)}}^T r_{(-l)}, \lambda_1\phi_l)^2] &= \mathbb{E}[\| \epsilon_1 \|_2^2 \ \mathbb{1}_{|\epsilon_1|>\lambda_1\phi_l}] - 2\lambda_1\phi_l\mathbb{E}[|\epsilon_1|\mathbb{1}_{|\epsilon_1|>\lambda_1\phi_l}] \\ &\quad + \lambda_1^2\phi_l^2\mathbb{E}[\mathbb{1}_{|\epsilon_1|>\lambda_1\phi_l}]\end{aligned} \tag{19}$$

$$\begin{aligned}\mathbb{E}[\| \epsilon_1 \|_2^2 \ \mathbb{1}_{|\epsilon_1|>\lambda_1\phi_l}] &= \mathbb{E}[\| \epsilon_1 \|_2^2 \ (1 - \mathbb{1}_{|\epsilon_1|\leq\lambda_1\phi_l})] \\ &= \lambda_1\phi_l^2(1 - \mathbb{E}[\| \epsilon_0 \|_2^2]\mathbb{1}_{|\epsilon_0|\leq 1}) \\ &\approx \lambda_1\phi_l^2(1 - (0.68 - 2\frac{1}{\sqrt{2\pi}}\exp(-0.5))) \\ &= (0.32 + \sqrt{\frac{2}{\pi}}\exp(-0.5))\lambda_1^2\phi_l^2\end{aligned} \tag{20}$$

$$\begin{aligned}\mathbb{E}[|\epsilon_1|\mathbb{1}_{|\epsilon_1|>\lambda_1\phi_l}] &= \lambda_1\phi_l\mathbb{E}[|\epsilon_0|\mathbb{1}_{|\epsilon_0|>1}] \\ &= \lambda_1\phi_l(\mathbb{E}|\epsilon_0| - \mathbb{E}|\epsilon_0|\mathbb{1}_{|\epsilon_0|\leq 1}) \\ &= \lambda_1\phi_l(\sqrt{\frac{2}{\pi}} - \sqrt{\frac{2}{\pi}}(1 - \exp(-0.5))) \\ &= \sqrt{\frac{2}{\pi}}\exp(-0.5)\lambda_1\phi_l\end{aligned} \tag{21}$$

$$\mathbb{E}[\mathbb{1}_{|\epsilon_1|>\lambda_1\phi_l}] = \mathbb{P}(|\epsilon_0| > 1) \approx 0.32 \tag{22}$$

Take equations 20 - 22 to equation 19, we can get

$$\mathbb{E}[S({X_2^{(l)}}^2 r_{(-l)}, \lambda_1\phi_l)^2] \approx (0.64 - \sqrt{\frac{2}{\pi}}\exp(-0.5))\lambda_1^2\phi_l^2 \tag{23}$$

Insert results of equation (23) into (18), we define

$$\psi_l = \sqrt{\parallel X_1^{(l)} \parallel_2 + \{0.64 - \sqrt{\frac{2}{\pi}}\exp(-0.5)\} \parallel X_2^{(l)} \parallel_2} \tag{24}$$

such that

$$\lambda_1^2 \psi_l^2 = \lambda_1^2 [\parallel X_1^{(l)} \parallel_2 + \{0.64 - \sqrt{\frac{2}{\pi}}\exp(-0.5)\} \parallel X_2^{(l)} \parallel_2] \tag{25}$$

Algorithms

Fast iterative shrinkage-thresholding algorithm with backtracking (*20*)

Proximal operator for group lasso (*21*)

Adaptive restart for rippling behavior (*22*)

Adaptive stepwise of cyclic Barzilai-Borwein spectral approach (*23*)

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initialization $\theta_0 = 0$ or warm start from previous run, $\tau_0 = 0.1$, stepsize $\eta = 0.5$;
while $i \leq k$ do
    $u_i = \theta_{i-1} - \tau_i \bigtriangledown f(\theta_{i-1})$ Find the smallest nonnegative integers $s_i$ such that with
      $\tau_i = \eta^{s_{i-1}} \tau_{i-1}$, $(f+g)(P_{\tau_i,g}(u_i)) \leq Q_{\tau_i,g}(P_{\tau_i,g}(u_i), u_i)$;
    Then, we compute $t_i = P_{\tau_i,g}(u_i)$ And accelarate the computation by setting if
      $f(\theta_i + g(\theta_i)) > f(\theta_{i-1}) + g(\theta_{i-1})$ then
        $\rho_i = 1$
    else
        $\rho_i = \frac{1+\sqrt{1+4\rho_{i-1}^2}}{2}$
    end
    $\theta_i = t_i + (\frac{\rho_{i-1}-1}{\rho_i})(t_i - t_{i-1})$ and find $\tau_{i+1}$ that $\tau_{i+1} I$ can mimic the Hessian $\bigtriangledown^2 f(\theta_i)$
end
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Algorithm 1: Patient Subgroup Identification Group Lasso Algorithm

Experiments

Signal to noise ratio: $SNR = \frac{Var(X\beta)}{Var(\epsilon)}$

Future Steps

check KKT condition

References and Notes

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