Generalized Group Elastic Net for Predictive Biomarker Identification

Wenxuan Deng[1]

[1]Department of Biostatistics, Yale University,

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 biomarkers. To show PEN has an supreme performance, this paper shows simulations in different scenerios and comparisons with several other variable selection methods.

1 Introduction

Prognostic biomarkers and predictive biomarkers.

Group lasso (*?*)

Elastic net (*?*) adaptive weights for elastic net (*?*)

Hierarchical Group lasso for interactions (*?*)

Overlapping group lasso (*?*) (*?*) (*?*)

Sparse Group Lasso (*?*) (*?*)

Structured group lasso (*?*) Group lasso for logistic regression (*?*)

Other variable selection methods:

GUIDE: a regression tree (*?*) (*?*)

SIS: screening (*?*) (*?*)

SIR: (*?*) (*?*)

Stepwise selection: (*?*)

2 Methods

2.1 Model

$$Y = X_0\beta_0 + X_T\beta_\tau + X_1\beta_1 + X_T \otimes X_1\beta_2 + \epsilon \tag{1}$$

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

$$X = [X_0, X_T, X_1^{(1)}, \ldots, X_m^{(1)}, X_T X_1^{(1)}, \ldots, X_T X_1^{(m)}] \tag{2}$$

and

$$\beta = [\beta_0, \beta_\tau, \beta_1^{(1)}, \ldots, \beta_1^{(m)}, \beta_2^{(1)}, \ldots, \beta_2^{(m)}] \tag{3}$$

For each gene l, its prognostic and predictive design matrix is denoted as $X^{(l)} = [X_1^{(l)}, X_2^{(l)}]$ where $X_2^{(l)} = X_T X_1^{(l)}$ and its corresponding coefficients are $\beta^{(l)} = [\beta_1^{(l)}, \beta_2^{(l)}]$

2.2 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

$$\min_{\beta} f(\beta|Y, X_0, X_T, X_1) + g(\beta) \tag{4}$$

$$g(\beta) = \lambda_1 \sum_i \phi_i |\beta_2^{(i)}| + \lambda_1 \sum_i \psi_i \sqrt{(\beta_1^{(1)})^2 + (\beta_2^{(1)})^2} + \lambda_2 (\| \beta_1 \|_2^2 + \| \beta_2 \|_2^2) \tag{5}$$

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.

2.3 Criterion and Adaptive Weights

2.3.1 KKT conditions

KKT (*?*)

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

$$X^{(l)^T}(Y - X^T\hat{\beta}) = \lambda_1\phi_l \begin{bmatrix} 0 \\ v \end{bmatrix} + \lambda_1\psi_l u + \frac{1}{2}\lambda_2\hat{\beta}^{(l)} \tag{6}$$

where

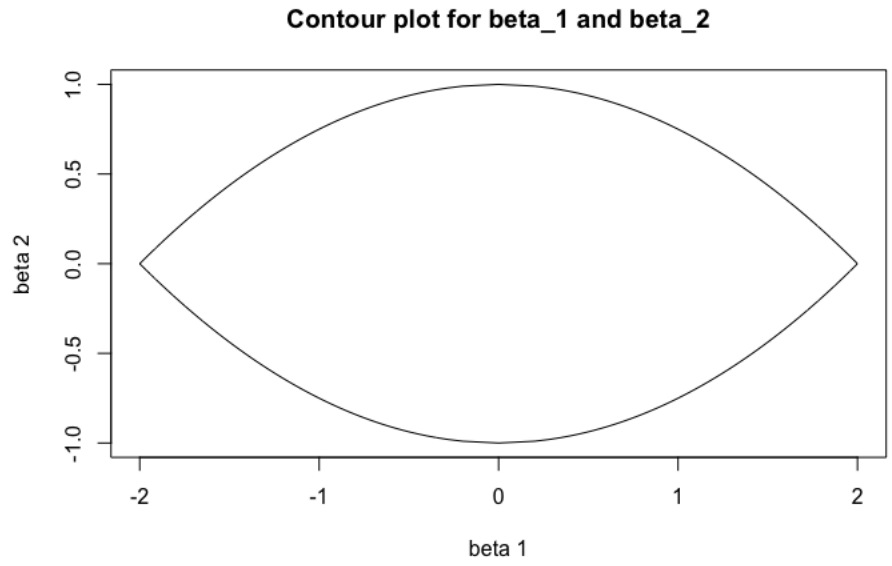


Figure 1: Geometrical interpretation of penalty function

$$v = \begin{cases} \text{sign}(\hat{\beta}_2^{(l)}) & \text{if } \hat{\beta}_2{}^{(l)} \neq 0 \\ \in \{v : |v|_1 \leq 1\} & \text{if } \hat{\beta}_2{}^{(l)} = 0 \end{cases} \tag{7}$$

$$u = \begin{cases} \hat{\beta}^{(l)} / \parallel \hat{\beta}^{(l)} \parallel_2 & \text{if } \hat{\beta}^{(l)} \neq 0 \\ \in \{u : \parallel u \parallel_2 \leq 1\} & \text{if } \hat{\beta}^{(l)} = 0 \end{cases} \tag{8}$$

- We now investigate when $\hat{\beta}^{(l)} = 0$ satisfies KKT condition **??**. We propose the following condition

$$S(X_1^{(l)^T} r_{(-l)}, 0)^2 + S(X_2^{(l)^T} r_{(-l)}, \lambda_1 \phi_l)^2 \leq \lambda_1^2 \psi_l^2 \tag{9}$$

where

$$S(z, a) = \text{sign}(z)(|z| - a)_+ \tag{10}$$

and

$$r_{(-l)} = Y - X^{(-l)^T}\hat{\beta}^{(-l)} \tag{11}$$

Under this condition, we can find

$$u = \begin{bmatrix} \frac{X_1^{(l)} r_{(-l)}}{\lambda_1 \psi_l} \\ \frac{S(X_2^{(l)^T} r_{(-l)}, \lambda_1 \phi_l)}{\lambda_1 \psi_l} \end{bmatrix} \tag{12}$$

$$v = \begin{bmatrix} 0 \\ \frac{X^{(l)^T} r_{(-l)} - S(X_2^{(-l)^T} r_{(-l)}, \lambda_1 \phi_l)}{\lambda_1 \psi_l} \end{bmatrix} \tag{13}$$

such that $\parallel u \parallel_2 \leq 1$ and $|v|_\infty \leq 1$. By simple algebra, the subgradient equation **??** was satisfied with $\hat{\beta}^{(l)} = 0$

- if KKT condition holds with $\hat{\beta}^{(l)} \neq 0$ but $\hat{\beta}_2^{(l)} = 0$, the KKT condition can be reformulated as following

$$X^{(l)^T}(Y - X^{(-I(l))^T}\hat{\beta}^{(-I(l))}) = \lambda_1 \phi_l \begin{bmatrix} 0 \\ v \end{bmatrix} + \lambda_1 \psi_l \frac{\hat{\beta}^{(l)}}{\parallel \hat{\beta}^{(l)} \parallel_2} + \frac{1}{2}\lambda_2 \hat{\beta}^{(l)} \tag{14}$$

To satisfy $\hat{\beta}_2^{(l)} = 0$ and KKT condtion, we should have

$$X_2^{(l)^T} r_{(-I(l))} \leq \lambda_1 \phi_l \tag{15}$$

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

- if KKT condition holds with $\hat{\beta}^{(l)} \neq 0$ as well as $\hat{\beta}_2^{(l)} \neq 0$, the KKT condition is reformulated as

$$X^{(l)^T}(Y - X^{(-I(l))^T}\hat{\beta}^{(-I(l))}) = \lambda_1 \phi_l \begin{bmatrix} 0 \\ \text{sign}(\hat{\beta}_2^{(l)}) \end{bmatrix} + \lambda_1 \psi_l \frac{\hat{\beta}^{(l)}}{\parallel \hat{\beta}^{(l)} \parallel_2} + \frac{1}{2}\lambda_2 \hat{\beta}^{(l)} \tag{16}$$

Then we get

$$\begin{aligned}\hat{\beta}_2^{(l)} &= \frac{{X_2^{(l)}}^T(Y - X^T\hat{\beta}^{(-I(l))}) - \lambda_1\phi_l \text{sign}(\hat{\beta}_2^{(l)})}{{X_2^{(l)}}^T X_2^{(l)} + \frac{\lambda_1\psi_l}{\|\hat{\beta}^{(l)}\|_2} + \frac{1}{2}\lambda_2} \\ &= \frac{S({X_2^{(l)}}^T r_{(-I(l))}, \lambda_1\phi_l)}{{X_2^{(l)}}^T X_2^{(l)} + \frac{\lambda_1\psi_l}{\|\hat{\beta}^{(l)}\|_2} + \frac{1}{2}\lambda_2}\end{aligned} \tag{17}$$

$$\hat{\beta}_1^{(l)} = \frac{{X_2^{(l)}}^T r_{(-G(l))}}{{X_1^{(l)}}^T X_1^{(l)} + \frac{\lambda_1\psi_l}{\|\hat{\beta}^{(l)}\|_2} + \frac{1}{2}\lambda_2} \tag{18}$$

$$\hat{\beta}_0 = \frac{X_0^T r_{(-0)}}{X_0^T X_0} \tag{19}$$

$$\hat{\beta}_\tau = \frac{X_T^T r_{(-T)}}{X_T^T X_T} \tag{20}$$

2.3.2 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 $\hat{\beta}_2^{(l)} = 0$. Let

$$\begin{aligned}\| {X_2^{(l)}}^T r_{(-I(l))} \|_2 &= \lambda_1\phi_l \\ E[({X_2^{(l)}}^T r_{(-I(l))})^2] &= \lambda_1^2\phi_l^2\end{aligned} \tag{21}$$

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

$$\phi_l \propto \| X_2^{(l)} \|_2 \tag{22}$$

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

On the other hand, based on inequality **??** and results from formula **??**, we let

$$\mathbb{E}[S(X_1^{(l)^T} r_{(-l)}, 0)^2 + S(X_2^{(l)^T} r_{(-l)}, \lambda_1 \phi_l)^2] = \lambda_1^2 \psi_l^2 \tag{23}$$

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 $\epsilon_0 = \epsilon_1 / \lambda_1 \phi_l \sim N(0, 1)$.

$$\begin{aligned} \mathbb{E}[S(X_2^{(l)^T} r_{(-l)}, \lambda_1 \phi_l)^2] = \mathbb{E}[\| \epsilon_1 \|_2^2 \, \mathbb{1}_{|\epsilon_1| > \lambda_1 \phi_l}] - 2\lambda_1 \phi_l \mathbb{E}[|\epsilon_1| \mathbb{1}_{|\epsilon_1| > \lambda_1 \phi_l}] \\ + \lambda_1^2 \phi_l^2 \mathbb{E}[\mathbb{1}_{|\epsilon_1| > \lambda_1 \phi_l}] \end{aligned} \tag{24}$$

$$\begin{aligned} \mathbb{E}[\| \epsilon_1 \|_2^2 \, \mathbb{1}_{|\epsilon_1| > \lambda_1 \phi_l}] &= \mathbb{E}[\| \epsilon_1 \|_2^2 \, (1 - \mathbb{1}_{|\epsilon_1| \leq \lambda_1 \phi_l})] \\ &= \lambda_1 \phi_l^2 (1 - \mathbb{E}[\| \epsilon_0 \|_2^2] \mathbb{1}_{|\epsilon_0| \leq 1}) \\ &\approx \lambda_1 \phi_l^2 (1 - (0.68 - 2 \frac{1}{\sqrt{2\pi}} \exp(-0.5))) \\ &= (0.32 + \sqrt{\frac{2}{\pi}} \exp(-0.5)) \lambda_1^2 \phi_l^2 \end{aligned} \tag{25}$$

$$\begin{aligned} \mathbb{E}[|\epsilon_1| \mathbb{1}_{|\epsilon_1| > \lambda_1 \phi_l}] &= \lambda_1 \phi_l \mathbb{E}[|\epsilon_0| \mathbb{1}_{|\epsilon_0| > 1}] \\ &= \lambda_1 \phi_l (\mathbb{E}|\epsilon_0| - \mathbb{E}|\epsilon_0| \mathbb{1}_{|\epsilon_0| \leq 1}) \\ &= \lambda_1 \phi_l (\sqrt{\frac{2}{\pi}} - \sqrt{\frac{2}{\pi}} (1 - \exp(-0.5))) \\ &= \sqrt{\frac{2}{\pi}} \exp(-0.5) \lambda_1 \phi_l \end{aligned} \tag{26}$$

$$\mathbb{E}[\mathbb{1}_{|\epsilon_1| > \lambda_1 \phi_l}] = \mathbb{P}(|\epsilon_0| > 1) \approx 0.32 \tag{27}$$

Take equations **??** - **??** to equation **??**, we can get

$$\mathbb{E}[S({X_2^{(l)}}^2 r_{(-l)}, \lambda_1\phi_l)^2] \approx (0.64 - \sqrt{\frac{2}{\pi}}\exp(-0.5))\lambda_1^2\phi_l^2 \tag{28}$$

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

$$\psi_l = \sqrt{\parallel X_1^{(l)} \parallel_2 + \{0.64 - \sqrt{\frac{2}{\pi}}\exp(-0.5)\} \parallel X_2^{(l)} \parallel_2} \tag{29}$$

such that

$$\lambda_1^2\psi_l^2 = \lambda_1^2[\parallel X_1^{(l)} \parallel_2 + \{0.64 - \sqrt{\frac{2}{\pi}}\exp(-0.5)\} \parallel X_2^{(l)} \parallel_2] \tag{30}$$

2.4 Algorithms

To optimize loss function **??**, we use proximal algorithm since penalty function **??** is not differential everywhere (***?***). Our algorithm also implements fast iterative shrinkage-thresholding algorithm with backtracking, adaptive restart for rippling behavior, and adaptive stepwise of cyclic Barzilai-Borwein spectral approach to accelarate convergence (***?***) (***?***) (***?***).

Let

$$Q_{\tau,g}(t,u) = \lambda_1\phi_l|t_2|_1 + \lambda_1\psi_l \parallel t \parallel_2 + \frac{1}{2\tau} \parallel t - u \parallel_2^2 \tag{31}$$

then the proximal operator is defined as

$$\tilde{t} = arg\min_t Q_{\tau,g}(t,u) \tag{32}$$

For convenience, we denote $P_{\tau,g}(u) = \tilde{t}$

To get $P_{\tau,g}(u)$, we propose the following lemma, which is generalized from fast Overlapping group lasso method (*?*).

Lemma 2.1. *Define proximal operator*

$$\pi_{\lambda_2}^{\lambda_1}(u) = arg\min_{t\in\mathbb{R}^2}\{g_{\lambda_2}^{\lambda_1}(t) \equiv \frac{1}{2\tau} \parallel t-u \parallel_2^2 +\lambda_1|t_2|_1 + \lambda_2 \parallel t \parallel_2\} \tag{33}$$

The the following equition holds

$$\pi_{\lambda_2}^{\lambda_1}(u) = \pi_{\lambda_2}^{0}(v) \tag{34}$$

where

$$\begin{aligned} v_1 &= u_1 \\ v_2 &= \textit{sign}(u_2)\max\{|u_2|_1 - \lambda_1, 0\} \\ \pi_{\lambda_2}^{0}(v) &= arg\min_{t\in\mathbb{R}^2}\{h_{\lambda_2}(t) \equiv \frac{1}{2\tau} \parallel t-v \parallel_2^2 +\lambda_2 \parallel t \parallel_2\} \end{aligned} \tag{35}$$

Proof. Assume $x^* = \pi_{\lambda_2}^{0}(v)$ and $\phi_{\lambda_2}^{\lambda_1}(x^*) = \lambda_1|x_2^*|_1 + \lambda_2 \parallel x^* \parallel_2$. Then

$$0 \in \partial h_{\lambda_2}(x^*) = x^* - v + \partial\phi_{\lambda_2}^{0}(x^*) \tag{36}$$

$$\partial g_{\lambda_2}^{\lambda_1}(x^*) = x^* - u + \partial\phi_{\lambda_2}^{\lambda_1}(x^*) \tag{37}$$

Because we have $-v+\partial\phi_{\lambda_2}^{0}(x^*) \in -u+\partial\phi_{\lambda_2}^{\lambda_1}(x^*)$, the above equations imply that $0 \in \partial g_{\lambda_2}^{\lambda_1}(x^*)$.

□

Therefore,

$$\begin{aligned} P_{\tau,g}(u) &= (1 - \frac{\lambda_2}{\parallel u \parallel_2})_+ v \\ v_1 &= u_1 \\ v_2 &= \text{sign}(u_1)\max\{|u_2| - \lambda_1\} \end{aligned} \tag{38}$$

Based on equation **??**, the algorithm framework is shown in Algorithm 1.

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 τ_{i+1} that $\tau_{i+1}I$ can mimic the Hessian $\bigtriangledown^2 f(\theta_i)$
end

Algorithm 1: Patient Subgroup Identification Group Lasso Algorithm

2.5 Cross Validation and Regularization Parameter

Appropriate regularization parameters, λ_1 and λ_2, are critical for variable selection. Previous lasso methods tend to use smallest Mean Error Square(MSE) for optimal regularization parameters. However, in this method, we will not use MSE anymore since that will result in overfitting although the model is simplified. So we used an arbitrary regularization parameters to select the top covariates. But in the future, we will develop an AIC-like approach that can balance the MSE and the model size of predictive effects.

3 Experiments

We conducted several experiments to inspect how PEN will perform under different simulation setup. Small sample size is very common in real clinical trial dataset. That results in small n and big p, where n is sample size and p is dimension. However, most of previous approaches used to set n as approximately 1000, which is too big to mimic a real clinical trial. In our experiments, we always assume sample size is as small as 100, i.e. $n = 100$.

On the other hand, the design matrix contains 5 baseline covariates, 1 treatment covariate

and p biomarkers, where p is ranged from $\frac{n}{2}$ to $2n$. Experiments with different p can help us identify how the ratio n and p will change the variable selection.

We also conducted different proportions of nonzero (1-sparsity) prognostic and predictive effects from 10% to 40% and 5% to 20%, respectively. Since PEN has a strong assumption of hierarchical structure between prognostic and predictive effects, the sparsity of predictive biomarker is always bigger than the sparsity of prognostic biomarkers, due to the reason that a biomarker is prognostic before it is predictive.

To test different signal to noise ratio (SNR), PEN did variable selection on different SNR, which is defined as $SNR = \frac{Var(X\beta)}{Var(\epsilon)}$.

Since the correlation among SNPs and biomarkers from the same pathway is common, we also assume a blockwise AR(1) correlation structure with $\rho = .3$, where the sizes of blocks are sampling from multinormial distribution where the mean for block size is 5.

	Proprotion	SNR	Dimension	SNP
# Predictive biomarkers	5%, 10%, 15%, 20%	10%	10%	10%
# Biomarkers	100	100	50, 100, 200	100
SNR	10	1, 5, 10, 20, 100	10	10
Covariate Type	N(0,1)	N(0,1)	N(0,1)	N(0,1) for baseline and treatment covariates; Binom(2,0.5) for genomics covariates

Table 1: Summary of Simulation Setup

All experiments of PEN ("glasso" in tables and figures) were compared with other standard variable selection methods: General Elastic Net without penalizing baseline and treatment variables (Lasso), Bayesian Model Averaging (BMA), Stepwise Variable Selection by likelihood (step), Iterative Sure Independent Screening (SIS) and Random Forest.

Table **??** shows the summary of different simulation setups we conducted. All cases were

run 100 times with fixed seed 1001-1100. The coefficients for baseline and treatment covariates are sampled from gaussian distribution while the coefficients for genomics covariates are constants and randomly picked up from ± 3 and ± 5.

Proportion of Nonzero Predictive Effects The proportion of nonzero predictive effects indicates the number of biomarkers which are relate with outcomes. Although PEN was applied on the simulation with 20% nonzero predictive effects, real datasets usually has much higher sparsity. Figure **??** shows a comprehensive analysis with different predictive effects sparsities. We inspected the results from several metrics: the difference between true and estimated parameters, sum square of errors (SSE), positive predictive value (PPV), false negative rate (FNR) and model size for only predictive biomarkers. Final goal for PEN is to enhance the variable selection accuracy only for predictive biomarkers, so PPV and FNR for predictive efffects are two mosrt important metrics. .

From Figure **??** and **??**, we observe that PEN always gets almost highest PPV in all different scenerios in the comparisons with other five methods. SIS can achieve a bit higher PPV when proportions are 15% and 20%. But it is still not reliable due to two reasons. Firstly, only proportion of $< 10\%$ is practical in real datasets. Cases of 15% and bigger imply too much significant biomarkers. Secondly, SIS has extremely high FNR whatever the proportion is. That is due to the limited number of top covariates SIS selects. As shown in Figure **??** (c), the estimated predictive biomarker model size of SIS are significantly below the ground truth and close to axis. The other observation is that PEN also has a slightly underestimated predictive effect model size. That is also the key reason why PEN does not achieve the lowest FNR. That is why our next step is to develop a new stop criterion. Because of the arbitrary values of regularization parameters, PEN tends to select fewer predictive biomarkers. Our future stop criterion should guarantee an unbiased predictive biomarker model size.

SNR Small SNR indicates large noise, e.g. half of the outcome variation can be explained

by the noise when SNR is as small as 1. The comprehensive data analysis and visualization of PPV, FNR and predictive biomarker model size curves are shown in Figure **??**, **??** and **??**. Similarly, PEN always gets the best performances in terms of PPV and FNR.

Dimension In this session, PEN was applied on difference cases when the number of biomarkers are 50, 100, and 200, respectively. PEN is unable to deal with ultra high-dimensional data so far with small sample size, i.e. $n = 100$. PEN even does not have a very promising performance even with moderate high-dimensional data, i.e. $p = 2n = 200$, although it is the most reliable method compared with other methods. The problem of underestimated model size still exists for PEN based on the results of Figure **??** (c).

Categorical Covariates For genetics data when covariates are SNPs, binomial distribution instead of gaussian distribution can better represent the distribution of biomarkers. Shown in Figure **??**, PEN has an overwhelming performance in the comparisons with the other five methods and its FNR is approximate 0.75, which is similar with the other approaches. That indicates PEN is still the most reliable one when the covariates are SNPs.

4 Discussion

In this project, we proposed a new method called PEN based on hierarchical group lasso and elastic net. The special penalty term design of PEN lets it have a hierarchical structure between prognostic and predictive effects, which could enhance the accuracy of predictive biomarker identification. Simulations on different scenerios have shown PEN is a reliable approach compared with other popular methods such as Elastic Net, SIS, and random forest. However, PEN can be further improved for a better performance. Firstly, a new stop criterion is needed for an unbiased predictive biomarker model size. To solve this problem, it is reasonable to combine prediction error or likelihood with the number of selected predictive biomarkers. Secondly, the hierarchical assumption is too strong and may not hold for some biomarkers. So we need to

conduct more experiments without such relationship. Thirdly, it is better to check whether our estimations satisfy KKT conditions or not. That will help us to undertand the results. Finally, adaptive weights could be improved for better estimations.

	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	20.094	109.746	417.007	0.779	0.61	0.742	0.92	0.568	0.694	3.32
lasso	20.264	112.605	415.909	0.728	0.636	0.771	0.681	0.64	0.628	5.61
Stepwise	20.139	109.993	414.014	0.806	0.597	0.845	0.757	0.6	0.591	5.54
SIS	22.399	125.715	434.41	0.736	0.853	0.785	0.654	0.854	0.851	2.3
Random Forest	24.626	153.615	436.781	0.237	0.86	0.297	0.14	0.833	0.915	6.33
BMA	27.834	183.012	436.781	0.155	0.891	NaN	0.155	1	0.674	21

(a) proportion = 5%

	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	16.569	93.874	353.888	0.641	0.359	0.63	0.688	0.288	0.502	7.36
lasso	17.89	106.679	341.056	0.569	0.431	0.663	0.458	0.44	0.411	12.98
Stepwise	23.341	150.19	312.545	0.454	0.546	0.557	0.333	0.544	0.552	13.56
SIS	22.866	129.041	427.122	0.747	0.874	0.769	0.657	0.876	0.871	1.99
Random Forest	24.375	159.322	411.028	0.318	0.648	0.373	0.242	0.637	0.67	13.7
BMA	38.888	279.686	411.028	0.116	0.884	NaN	0.116	1	0.653	30

(b) proportion = 10%

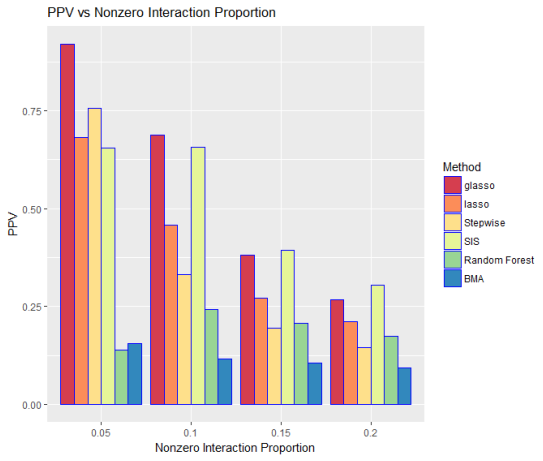
	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	18.472	117.706	345.981	0.444	0.333	0.466	0.381	0.231	0.538	12.13
lasso	20.114	133.778	340.223	0.375	0.437	0.451	0.272	0.418	0.475	19.34
Stepwise	27.439	195.657	338.083	0.271	0.594	0.34	0.194	0.594	0.592	21.13
SIS	23.459	134.417	436.151	0.492	0.92	0.528	0.394	0.922	0.917	2.03
Random Forest	26.293	184.904	388.71	0.284	0.545	0.345	0.208	0.539	0.557	21.33
BMA	36.442	260.38	388.71	0.105	0.895	NaN	0.105	1	0.685	30

(c) proportion = 15%

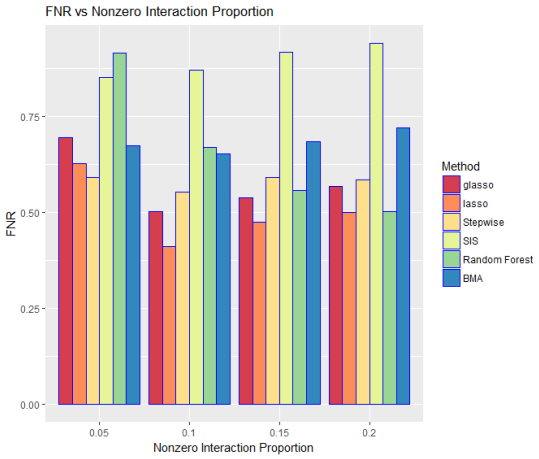
	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	20.774	143.908	325.852	0.371	0.258	0.409	0.267	0.103	0.568	16.26
lasso	20.465	143.565	322.515	0.357	0.286	0.452	0.212	0.179	0.499	23.76
Stepwise	30.438	233.134	334.807	0.207	0.586	0.263	0.146	0.587	0.584	28.49
SIS	23.765	137.029	440.872	0.407	0.943	0.433	0.305	0.944	0.941	1.78
Random Forest	31.202	239.743	367.004	0.23	0.517	0.276	0.174	0.524	0.503	28.53
BMA	35.273	251.139	367.004	0.093	0.907	NaN	0.093	1	0.721	30

(d) proportion = 20%

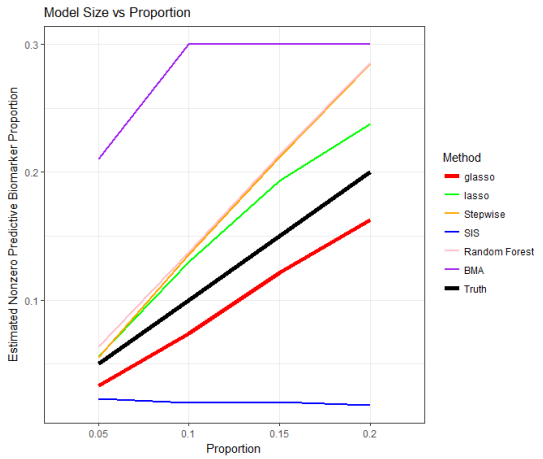
Figure 2: Tables for different proportion when fixing the number of biomarkers as 100, SNR as 10, and continuous covariate type. The proportions of nonzero predictive effects are 5%, 10%, 15%, and 20%. L2 = mean $\| \hat{\beta} - \beta \|_2$, L1 = mean $\| \hat{\beta} - \beta \|_1$, SSE = Sum Square of Errors, PPV = Positive Predictive Value, FNR = False Negative Rate, num = Model Size, all = across both prognostic and predictive biomarkers, prog = across only prognostic biomarkers, pred = across only predictive biomarkers



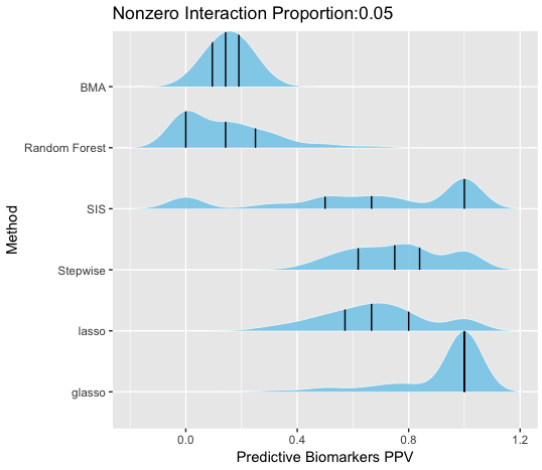
(a) Precision of Predictive Biomarkers Selection



(b) FNR of Predictive Biomarkers Selection



(c) Model Size of Predictive Biomarkers



(d) Distribution of predictive biomarker selection precision when proportion=5% over 100 Independent simulations.

Figure 3: performance of PEN with different proportions of nonzero predictive effects.

	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	29.203	185.008	458.579	0.401	0.599	0.403	0.398	0.534	0.727	6.81
lasso	29.662	190.869	460.737	0.343	0.657	0.432	0.245	0.658	0.654	14.19
Stepwise	30.925	203.484	463.265	0.266	0.734	0.334	0.195	0.742	0.719	14.36
SIS	24.602	140.732	485.276	0.516	0.936	0.59	0.423	0.937	0.933	1.73
Random Forest	32.225	215.563	458.783	0.258	0.71	0.334	0.168	0.694	0.74	15.48
BMA	33.314	229.804	458.783	0.101	0.899	NaN	0.101	1	0.696	30

(a) SNR = 1

	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	20.369	118.955	405.68	0.575	0.425	0.564	0.623	0.356	0.561	7.15
lasso	20.324	118.592	405.601	0.58	0.42	0.679	0.429	0.38	0.5	11.75
Stepwise	23.58	146.84	418.518	0.41	0.59	0.493	0.314	0.596	0.577	13.54
SIS	23.119	130.447	451.972	0.689	0.889	0.767	0.563	0.892	0.884	2.12
Random Forest	25.502	167.541	420.195	0.307	0.661	0.373	0.218	0.644	0.696	14.05
BMA	28.263	196.45	420.195	0.113	0.887	NaN	0.113	1	0.662	30

(b) SNR = 5

	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	16.569	93.874	353.888	0.641	0.359	0.63	0.688	0.288	0.502	7.36
lasso	17.89	106.679	341.056	0.569	0.431	0.663	0.458	0.44	0.411	12.98
Stepwise	23.341	150.19	312.545	0.454	0.546	0.557	0.333	0.544	0.552	13.56
SIS	22.866	129.041	427.122	0.747	0.874	0.769	0.657	0.876	0.871	1.99
Random Forest	24.375	159.322	411.028	0.318	0.648	0.373	0.242	0.637	0.67	13.7
BMA	38.888	279.686	411.028	0.116	0.884	NaN	0.116	1	0.653	30

(c) SNR = 10

Figure 4: Tables for different SNR when fixing the number of biomarkers as 100, proportion as 10%, and continuous covariate type. The proportions of nonzero predictive effects are 1, 2, 5, and 10.

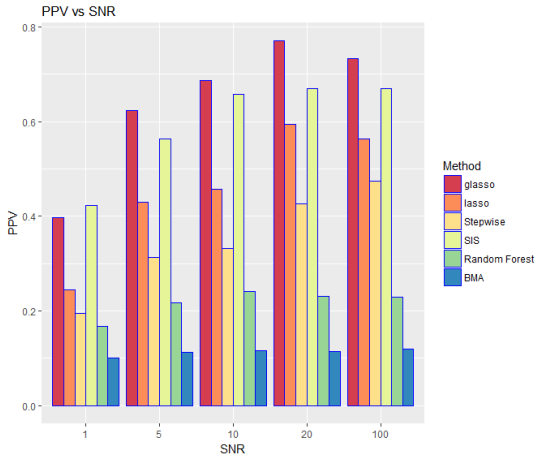
	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	21.375	119.795	402.598	0.317	0.704	0.695	0.771	0.456	0.599	5.34
lasso	21.819	123.663	406.793	0.292	0.741	0.764	0.595	0.544	0.535	8.04
Stepwise	19.56	114.27	391.578	0.536	0.464	0.625	0.427	0.462	0.468	12.77
SIS	22.591	126.135	440.827	0.767	0.862	0.818	0.67	0.866	0.852	2.09
Random Forest	23.955	155.791	407.54	0.327	0.64	0.395	0.231	0.618	0.684	13.64
BMA	27.266	188.004	407.54	0.115	0.885	NaN	0.115	1	0.654	30

(a) SNR = 20

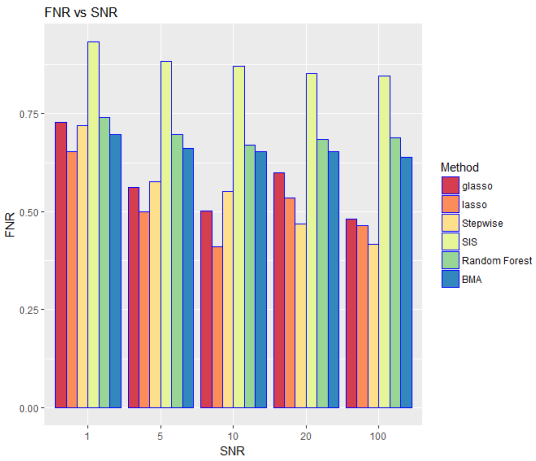
	L2	L1	SSE	PPV all	FNR all	PPV prog	PPV pred	FNR prog	FNR pred	num pred
glasso	15.856	84.172	364.794	0.695	0.305	0.683	0.734	0.218	0.481	7.09
lasso	15.112	78.803	359.894	0.73	0.27	0.812	0.563	0.173	0.465	9.62
Stepwise	18.135	103.565	377.448	0.591	0.409	0.686	0.474	0.405	0.417	12.68
SIS	22.477	126.001	437.874	0.743	0.856	0.781	0.67	0.86	0.847	2.29
Random Forest	23.437	151.734	402.414	0.33	0.638	0.4	0.23	0.612	0.689	13.57
BMA	26.617	182.727	402.414	0.12	0.88	NaN	0.12	1	0.639	30

(b) SNR = 100

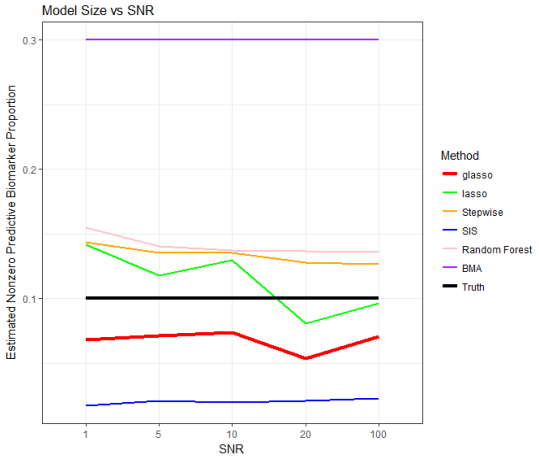
Figure 5: Tables for different SNR when fixing the number of biomarkers as 100, proportion as 10%, and continuous covariate type. The proportions of nonzero predictive effects are 20 and 100.



(a) Precision of Predictive Biomarkers Selection

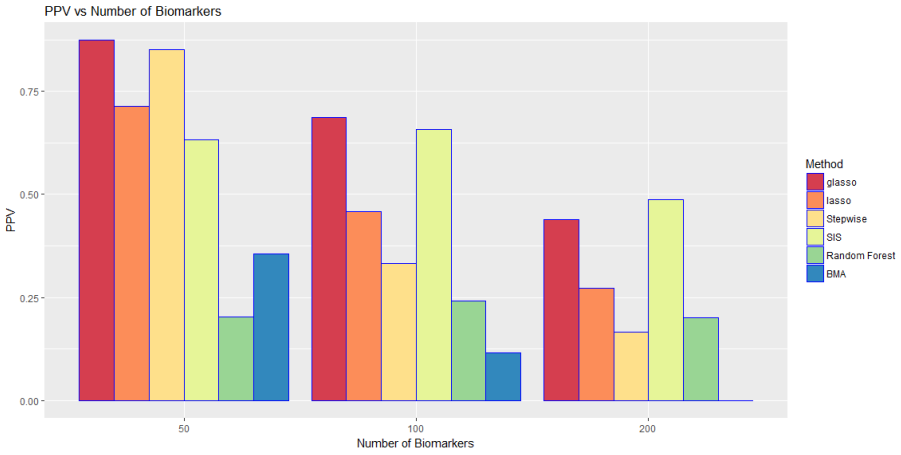


(b) FNR of Predictive Biomarkers Selection

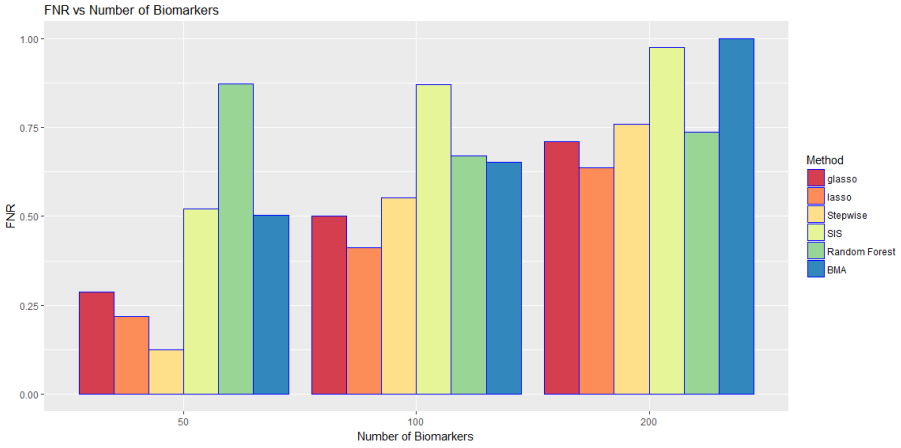


(c) Model Size of Predictive Biomarkers

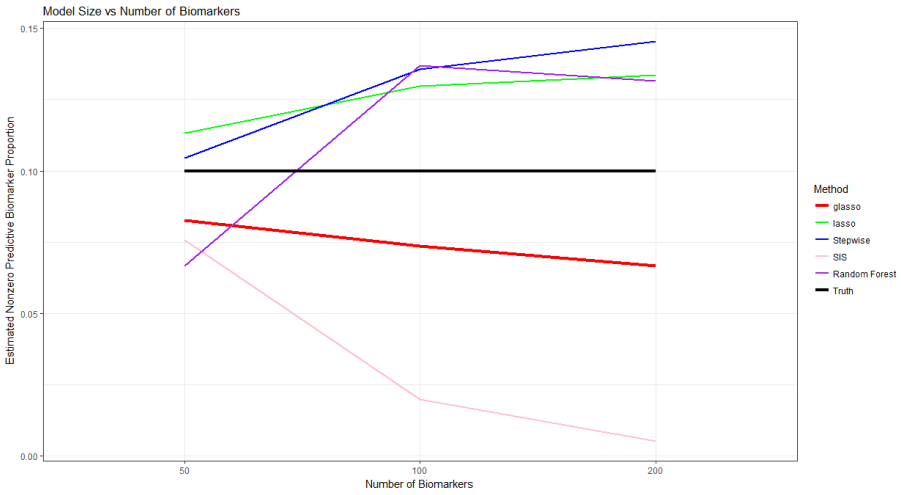
Figure 6: performance of PEN with different SNR.



(a) Precision of Predictive Biomarkers Selection

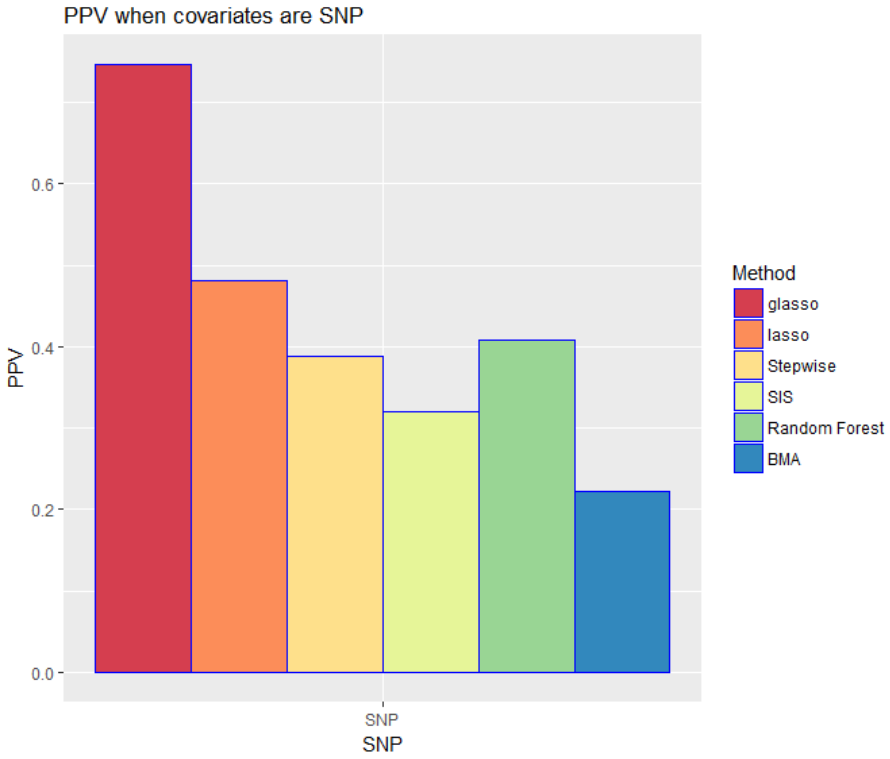


(b) FNR of Predictive Biomarkers Selection

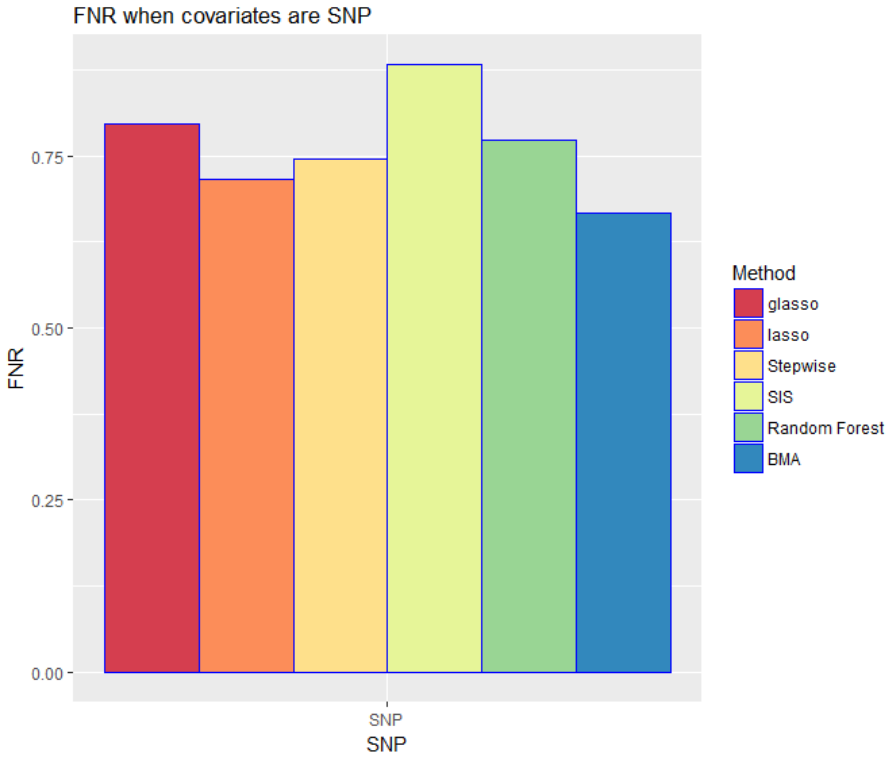


(c) Model Size of Predictive Biomarkers

Figure 7: performance of PEN with different numbers of biomarkers.



(a) Precision of Predictive Biomarkers Selection



(b) FNR of Predictive Biomarkers Selection

Figure 8: performance of PEN with SNPs as genomics covariates.