Mixture Network Regularization of Generalized Linear Model With Application in Genomics Data

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Abstract

High dimensional genomics data in biomedical sciences is an invaluable resource for constructing statistical prediction models. With the increasing knowledge of gene networks and pathways, such information can be utilized in the statistical models to improve prediction accuracy and enhance model interpretability. However, in certain scenarios the network structure may only be partially known or subject to inaccuracy. Thus, the performance of statistical models incorporating such network structure may be compromised. In this paper, we propose a weighted sparse network learning method by optimally combining a data driven network with sparsity property to prior known or partially known network to address this issue. We show that our proposed model attains the oracle property and achieves a parsimonious structure in high dimensional setting for different types of outcomes including continuous, binary and survival data. Simulations studies show that our proposed model is robust and outperforms existing methods. Case study on melanoma gene expression further demonstrates that our proposed model achieves good operating characteristics in identifying informative genes and predicting survival risk. An R package `glmaag` implementing our method is available on the Comprehensive R Archive Network (CRAN).

Keywords: mixture network regularization, stability selection, high dimensional variable selection, oracle and group property

1 Introduction

The rapid advancement in high throughput genomics profiling has revolutionized biomedical research towards personalized medicine for treating and preventing various diseases such as cancer. Several consortia have been established as part of the collaborative efforts to decipher the molecular mechanisms underlying these diseases, for example the Cancer Genome Atlas (TCGA) project have enabled researchers to access the rich genomics database. Together with the rapid development of machine learning and artificial intelligence, these databases have been utilized extensively to improve computational and statistical model building and predictions (Ma et al. (2010); Fan et al. (2019); Sun et al. (2019)).

One key attribute of these dataset is the high dimensionality, i.e., $p \gg n$ in which the number of candidate features/predictors (p) is much larger than the sample size (n). For instance, in a typical DNA methylation data, several hundred-thousand of CpGs are interrogated. Regularization framework has emerged as an attractive alternative to address the limitations of classical feature selection method in generalized linear models (GLM). For instance, GLM regularization with l_1 penalty (least absolute shrinkage and selection operator (LASSO)) Tibshirani (1996, 1997) allows for simultaneous variable selection to prevent overfitting, whereas Zou and Hastie (2005) showed that combining l_1 with l_2 penalty (elastic net (EN)) not only provides variable selection property but also robustness on correlated features (group property). Fan and Li (2001) and Fan et al. (2004) argued that a good feature selection procedure should have the oracle property which includes feature selection accuracy and asymptotically unbiased parameters estimation. Zou (2006) and Zou and Zhang (2009) proposed adaptive LASSO and adaptive EN that enjoy oracle property and can be optimized efficiently.

The aforementioned methods have been shown to achieve positive performance in prediction models in which no prior knowledge is available. However, the abundance of genomics research has enabled biological knowledge associated with the diseases to be inferred from gene regulatory networks and pathways. Several well-known databases of gene regulatory networks include the KEGG: Kyoto Encyclopedia of Genes and Genomes (`https://www.genome.jp/kegg/`) (Kanehisa and Goto (2000)) and the Reactome Pathways (`https://reactome.org/`). Many researchers are also actively reporting newly discovered networks and contributing updated information to the medical and biological fields (Li et al., 2018; Wu et al., 2018; Fan et al., 2019, 2020; Sun et al., 2019; Ma et al., 2020). If the network structure of the data is known in advance, one can potentially improve the model prediction and interpretability by incorporating the prior network information. In fact, in the analysis of gene expression data, network-based methods, which take a system perspective, have been shown to be more informative and powerful than individual-gene-based analysis. In general graph/network models can help us understand how variables are associated with each other (Ma et al., 2011; Fan et al., 2016). Such analysis not only can lead to a better understanding of the underlying data generating mechanisms but also serve as the building block of downstream analysis, such as unsupervised clustering and supervised regression analysis. Extensive methodological, computational, and theoretical research has been conducted on network methods (Wu et al., 2018; Ma et al., 2020; Fan et al., 2020). One possible extension is to replace the l_2 penalty with a quadratic penalty that utilizes the unsigned or signed adaptive Laplacian matrix of the network structure (Li and Li (2008, 2010)). This framework has been applied to both binary classification (Sun and Wang (2012)) and censored survival (Sun et al. (2014)) outcomes. On the other hand, Yang and Yi (2015) adapted the l_1 penalty with unsigned network penalty to achieve the

oracle property in Gaussian regression framework.

Although the aforementioned public regulatory network databases are invaluable prior knowledge, one limitation is that most of the known networks only present the connectivity and do not offer information on the strengths of the connectivity. The connection strengths in the network are important factors which may influence the group property of the prediction model. In addition, oftentimes a dataset has unknown or partially known network structure. In this scenario, one can still apply the graph based method by estimating the network empirically from the data, e.g., the neighborhood selection method (Meinshausen and Bühlmann, 2006) to learn the connectivity among the candidate features and use the reliability score provided by reference gene association (RGA) (Ucar et al., 2007) as the strengths of connectivity.

Another challenge in regularization framework is to correctly tune the penalty parameters. A common approach is via cross validation, which is straightforward to apply in penalized estimation. However, the cross validation approach has the tendency to overfit the data when the number of features are relatively large compared to the sample size (Wasserman and Roeder (2009)). An alternative approach is via the stability selection method (Meinshausen and Bühlmann (2010)) developed based on the consistency of variable selection across multiple subsamples, and this method has been shown to perform well in graph-based models (Liu et al. (2010)).

In this paper, we address the limitations of existing network/graph-based prediction models by proposing a mixture network prediction framework that combines two candidate networks: one being a fixed network obtained from gene regulatory network database while the other one is estimated from the data. To this end, we adapt the l_1 penalty in order to achieve sparse solutions with the oracle property. In addition, to attain a robust

variable selection accuracy, we implement the stability selection method for parameter tuning and compared this approach to the cross validation method. We develop our proposed framework for various outcomes including continuous, binary and survival data.

This paper is organized as follows. The description of our proposed method and the corresponding model fitting algorithm are provided in Section 2. Section 3 presents the statistical properties. The Monte Carlo simulations and case study are provided in Section 4 and 5, respectively. We conclude with a discussion in Section 6.

2 Methodology

2.1 Network Regularized Regression

We start our exposition by reviewing the method associated with the (partial) log likelihood $l(\beta)$ of generalized linear model (GLM) for continuous, binary and survival outcomes.

$$l(\beta) \propto \begin{cases} -\frac{1}{2}\sum_{i=1}^{n}\left(y_i - \beta_0 - x_i^T\beta\right)^2 & \text{Gaussian} \\ \sum_{i=1}^{n}\left[y_i\left(\beta_0 + x_i^T\beta\right) - \ln\left(1 + \exp\left(\beta_0 + x_i^T\beta\right)\right)\right] & \text{Logistic} \\ \sum_{i=1}^{n}\delta_i\left[x_i^T\beta - \ln\left(\sum_{j\in R_i}\exp\left(x_j^T\beta\right)\right)\right] & \text{Cox} \end{cases}$$

where $Y = (y_1, \cdots, y_n)^T$ denotes the outcome, $x_i = (x_{i1}, \cdots, x_{ip})^T$, $X = (x_1, \cdots, x_n)^T$ is the $n \times p$ predictors matrix. For Cox model, y_i is defined as the observed survival time for the ith patient which is subject to right censoring, δ_i is the event indicator, and $R_i = \{j | y_j \geq y_i\}$ is the risk set of subject i. None of these GLM models can be directly optimized in high dimensional ($p \gg n$) case. One approach to circumvent this challenge is to solve the maximum penalized (partial) likelihood estimator (MPLE).

We assume that the relationships among the covariates are specified by a network (graph) $G = (V, E)$, where $V = \{1, ..., p\}$ is the set of nodes corresponding to the p covariates, an element (i, j) in the edge or connectivity set $E \subset V \times V$ indicates a link between vertices i and j. For simplicity, we assume that G contains no loops or multiple edges. We propose a network LASSO with l_1 adaptive weights, in which the MPLE in primal form is given as below

$$\max \{l(\beta)\}, \text{ subject to } s_1 \sum_{i=1}^{p} w_i |\beta_i| + s_2 |\beta|^T L |\beta| \leq t \tag{1}$$

where $w = (w_1, \cdots, w_p)^T \succeq 0$ is the weight vector for l_1 penalty, L is the normalized Laplacian matrix, and $s_1 \geq 0$, $s_2 \geq 0$ and $t > 0$ are tuning parameters.

We suggest the following specification for (1). First, to estimate the signed adapter for the network penalty we first fit the GLM model without penalty or ridge GLM model with an l_2 penalty, and use the estimated signs of such initial estimators $\tilde{\beta}_{(1)}$ as the signed estimate (Sun et al. (2014)). Therefore, we have $|\beta|^T L |\beta| \approx \beta^T \text{diag}\left\{\text{sgn}\left(\tilde{\beta}_{(1)}\right)\right\} L \text{diag}\left\{\text{sgn}\left(\tilde{\beta}_{(1)}\right)\right\} \beta \triangleq \beta^T \hat{L} \beta$ and use $\hat{L}$ as the signed network. Next, to specify the weight vector w we can obtain an estimator $\tilde{\beta}_{(2)}$ by solving (1) where $s_1 = 0$ (no l_1 penalty). The l_1 adapted weights w can be estimated by $\hat{w} = \frac{1}{\tilde{\beta}_{(2)}}$ (Zou (2006) and Zou and Zhang (2009)). The normalized Laplacian matrix L is given by

$$L_{ij} = \begin{cases} 1 & i = j \\ -\omega_{ij}/\sqrt{\xi_i \xi_j} & i \neq j, \ (i, j) \in E \\ 0 & else \end{cases}$$

where E is the connectivity set including all connected pairs, ξ_i is the degree of the ith node and ω_{ij} is the strength (can be either positive or negative) of the connectivity between i

and j which can be estimated from the co-expression network utilizing the reliability score of Pearson correlation (Ucar et al. (2007)). The reliability score of feature i and j denoted as R_{ij} is given by $R_{ij} = \frac{1}{r_{ij} r_{ji}}$ where r_{ij} is the ranking of correlation between feature i and j among all the correlation of feature i to others.

We require L to be positive definite since $X^T X$ is not invertible. If L is an identity matrix, it reduces to adaptive elastic network model. This indicates that adaptive elastic net (Zou and Zhang (2009)) is a special case of (1) when there is no connection in the network (i.e., independent structure).

To solve equation (1), we consider optimizing the equivalent objective function

$$\max \left\{ \frac{1}{n} l(\beta) - \lambda_1 \sum_{i=1}^{p} w_i |\beta_i| - \frac{\lambda_2}{2} |\beta|^T L |\beta| \right\} \tag{2}$$

where $\lambda_1 \geq 0$ and $\lambda_2 \geq 0$.

To solve equation (2) when $\lambda_1 > 0$, we implement the proximal Newton based coordinate ascent algorithm derived by Friedman et al. (2010) and Simon et al. (2011) with adaptive l_1 penalty. For Gaussian regression, the coordinate-wise update is given by

$$\tilde{\beta}_j^{(t+1)} \leftarrow \frac{S\left(n^{-1} \sum x_{ij} \left(y_i - \tilde{\beta}_0 - \sum_{k \neq j} x_{ik} \tilde{\beta}_k^{(t)}\right) - \lambda_2 \sum_{k \neq j} \hat{L}_{jk} \tilde{\beta}_k^{(t)},\ \lambda_1 w_j\right)}{n^{-1} \sum_{i=1}^{n} x_{ij} + \lambda_2 \hat{L}_{jj}}$$

for the jth component at the tth iteration, where $S(a, b) = \text{sign}(a) (|a| - b)_+$ is the soft-thresholding operator (Donoho and Johnstone (1994)).

For logistic and Cox regression, we require a quadratic approximation of the (partial) log likelihood using secondary Taylor expansion given by

$$\tilde{l}(\beta) = \frac{1}{2} (z - \beta_0 \mathbf{1} - X\beta)^T l_\eta'' (z - \beta_0 \mathbf{1} - X\beta) + C\left(\eta, \tilde{\beta}\right)$$

where $z = \eta - \left(l_\eta''\right)^{-1} l', \eta = \tilde{\beta}_0 \mathbf{1} + X\tilde{\beta}$, $C\left(\eta, \tilde{\beta}\right)$ is a term independent of β, $\tilde{\beta}$ is the working update of β, and $\beta_0 = 0$ for Cox model. For Cox model we only need to calculate

the diagonal entries of l_η'' and fix all the off-diagonal entries to be zeros. This simple setting tends to speed up the computation based on the argument of Simon et al. (2011) where the off-diagonal entries of l_η'' are small compared to the diagonal entries. For logistic model l_η'' is already in a diagonal matrix form. Therefore, let u be the diagonal elements of l_η''. We have the approximate log likelihood function as

$$l_Q(\beta) = -\frac{1}{2}\sum_{i=1}^{n} u_i \left(z_i - \beta_0 - x_i^T\beta\right)^2$$

Note that the Gaussian model is a special case in which $u_i = 1$ and $z_i = y_i$. The coordinate-wise update step for logistic model is given by

$$\tilde{\beta}_j^{(t+1)} \leftarrow \frac{S\left(A - B,\ \lambda_1 w_j\right)}{n^{-1}\sum_{i=1}^{n} u_i^{(t)} x_{ij}^2 + \lambda_2 \hat{L}_{jj}}. \tag{3}$$

$$A = n^{-1}\sum_{i=1}^{n} u_i^{(t)} x_{ij}\left(z_i^{(t)} - \tilde{\beta}_0^{(t)} - \sum_{k\neq j} x_{ik}\tilde{\beta}_k^{(t)}\right)$$

$$B = \lambda_2 \sum_{k\neq j} \hat{L}_{jk}\tilde{\beta}_k^{(t)}$$

The working update for logistic model is given by

$$z_i^{(t)} = \tilde{\beta}_0 + x_i^T\tilde{\beta} + \frac{y_i - \mu_i^{(t)}}{\mu_i^{(t)}\left(1 - \mu_i^{(t)}\right)}$$

$$u_i^{(t)} = \mu_i^{(t)}\left(1 - \mu_i^{(t)}\right)$$

$$\mu_i^{(t)} = \frac{1}{1 + \exp\left(-X\tilde{\beta}^{(t)}\right)}.$$

For Cox model, we use Breslow's (Breslow (1972)) method to handle tied survival times. The working update is given by

$$z_i^{(t)} = \eta_i^{(t)} + \frac{1}{u_i^{(t)}} \left[\delta_i - \sum_{j \in C_i} \frac{d_i e^{\eta_i^{(t)}}}{\sum_{k \in R_j} e^{\eta_k^{(t)}}} \right]$$

$$u_i^{(t)} = \sum_{j \in C_i} d_i \frac{e^{\eta_i^{(t)}} \left[\sum_{k \in R_j} e^{\eta_k^{(t)}} - e^{\eta_i^{(t)}} \right]}{\left[\sum_{k \in R_j} e^{\eta_k^{(t)}} \right]^2}$$

$$\eta^{(t)} = X \tilde{\beta}^{(t)}$$

where R_j is the set of k for the jth sample with $t_k \geq t_j$, $C_i = \{j | t_j \leq t_i\}$ is the set of j for the ith sample with $t_j \leq t_i$ and d_i is the number of tied samples in survival time for the ith sample.

2.2 Mixed Network Tuning

In real data analysis, obtaining the correct complete network structure could be infeasible for fitting the model. In addition, even if the network structure is known, the strengths/weights of the connection might not be available. To circumvent these issues, we propose a mixture network method that combines a pre-specified network L_1 and a data driven network L_2 in the following penalized likelihood framework

$$\max \left\{ \frac{1}{n} l(\beta) - \lambda_1 \sum_{i=1}^{p} w_i |\beta_i| - \frac{\lambda_2}{2} |\beta|^T (cL_1 + (1-c) L_2) |\beta| \right\}$$

where $0 \leq c \leq 1$ is the network weight. If L_1 and L_2 are both positive definite, the final mixed network $L = cL_1 + (1-c) L_2$ is also positive definite, hence consistency property still holds. To obtain the network weight c we recommend to fix $\lambda_1 = 0$ when

tuning the weight between networks and only search for the combination of (λ_2, c) for computational efficiency. As suggested by Chen et al. (2015), we search λ_2 over the grid values $\{0.01 \times 2^0, 0.01 \times 2^1, \cdots, 0.01 \times 2^7\}$. To tune the parameter c, we recommend searching over $\{0, 0.1, 0.2, \cdots, 1\}$. We tune the two networks via cross validation method across the grid values of (λ_2, c) and chose the value of c that optimizes the cross validation performance. Upon identifying the optimal c we fix the final mixed network as $\hat{L} = cL_1 + (1-c)\, L_2$ when further tuning λ_1 and λ_2.

Numerous methods have been proposed for estimating high dimensional undirected graphs from data (Meinshausen and Bühlmann, 2006; Friedman et al., 2008; Liu et al., 2009, 2012) which were implemented in the R package `huge` (Zhao et al. (2012)). In this paper, we estimate a data-driven network L_2 by first obtaining the connectivity using the penalized neighborhood selection method (Meinshausen and Bühlmann (2006)) tuned by rotation information criterion (RIC). In the second step, we estimate the strengths/weights of connectivity using the reliability score provided by the reference gene association network (Ucar et al. (2007)).

2.3 Parameter Tuning

We compare two frameworks for tuning λ_1 and λ_2. The first is the cross validation (CV) framework, where we perform the CV via deviance $(\hat{l}\,(\text{full}) - \hat{l}\,(\text{train}))$ or robust measure including negative mean absolute error (MAE) for Gaussian, area under the receiver operating characteristic curve (AUC) for logistic, and concordance index (C) for Cox model. For Gaussian model, the deviance measure is equivalent to negative mean squared error (MSE). One can either use the maximum (max) rule, i.e., obtaining (λ_1, λ_2) that maximizes the CV measure or the one standard error (1se) rule, i.e., obtaining (λ_1, λ_2) that results in

the most parsimonious model within one standard error of the optimal CV. We also impose a $p/2$ constraint on the number of variables to improve computational speed.

Although CV is a convenient framework and has been shown to achieve good performance in low dimensional data, it may result in overfitting in high dimensional case (Wasserman and Roeder (2009)). An alternative approach is via the stability selection (SS) proposed by Meinshausen and Bühlmann (2010) which measures the feature selection stability across subsampling replicates, which has been shown to be robust in graphical model (Liu et al. (2010)).

Suppose we randomly draw K samples (usually $K = 100$) with $\lfloor n/2 \rfloor$ or $\lfloor 10\sqrt{n} \rfloor$ observations depending on the sample size as suggested by Meinshausen and Bühlmann (2010) and Liu et al. (2010), the selection probability of feature j is given by

$$\hat{P}^{\lambda_1,\lambda_2}(j) = \frac{1}{K}\sum_{k=1}^{K} I\left(\hat{\beta}_j^{\lambda_1,\lambda_2}(S_k)\right)$$

where S_k denotes the kth subsample and $\hat{\beta}_j^{\lambda_1,\lambda_2}(S_k)$ is the estimated coefficient for S_k with tuning parameters λ_1 and λ_2. The the selection variance is given by

$$\hat{\text{var}}^{\lambda_1,\lambda_2}(j) = \hat{P}^{\lambda_1,\lambda_2}(j)\left[1 - \hat{P}^{\lambda_1,\lambda_2}(j)\right].$$

A stable method should have a low selection variance. We define the instability score across all features as

$$\hat{IS}(\lambda_1,\lambda_2) = \frac{2}{p}\sum_{j=1}^{p} \hat{\text{var}}^{\lambda_1,\lambda_2}(j).$$

To make the score comparable across different λ_2's, we consider a monotone transformation of the instability score for each fixed λ_2 given by

$$\bar{IS}(\lambda_1,\lambda_2) = \sup_{x \geq \lambda_1} \hat{IS}(x,\lambda_2)$$

such that the instability path decreases with increasing λ_1 for each fixed λ_2. By combining all the instability scores together, we find the maximum score below a specific cutoff, e.g., 0.15 and use the corresponding (λ_1, λ_2) as the selected tuning parameter.

Tuning λ_1 and λ_2 usually operates iteratively by searching λ_1 for each fixed λ_2 until all possible values of (λ_1, λ_2) are considered. According to the strong rules for discarding predictors (Tibshirani et al. (2012)), it is not necessarily to consider all predictors for every λ_1. For every fixed λ_2, we discard predictors that are not likely to be retained in the model by checking the Karush-Kuhn-Tucker (KKT) condition.

At each iteration, if we have searched $\lambda_1^{(k)}$, the strong rule claims that the variables satisfy

$$\left| l_j' \left(\hat{\beta} \left(\lambda_1^{(k)} \right) \right) - \lambda_2 \tilde{L}_j \hat{\beta}_j \left(\lambda_1^{(k)} \right) \right| \geq \left(2\lambda_1^{(k+1)} - \lambda_1^{(k)} \right) \hat{w}_j$$

are of high probability to be selected by the model. Let V to be set of all these variables and V^c to be the complement set. What we need to do is to first try all the variables and obtain $\hat{\beta} = \left(\hat{\beta}_V, 0 \right)$. Then we can check whether $\hat{\beta}$ satisfy KKT condition, i.e.,

$$\left| l_j' \left(\hat{\beta} \right) - \lambda_2 \tilde{L}_j \hat{\beta}_j \right| \leq \lambda_1^{(k+1)} \hat{w}_j. \tag{4}$$

If $\hat{\beta}$ passed the KKT condition for all elements, $\hat{\beta}$ will just be the estimation of β for $\lambda_1^{(k+1)}$. Otherwise let U be the set for variables that does not pass KKT condition and let $V \leftarrow V \cup U$ and V^c be the complement set. We refit the model for V until all variables pass KKT condition. Specifically, the jth predictor is discarded from the optimization if it satisfies Equation 4. In the following study we adopt the strong rules in our model to improve computational speed.

3 Theoretical Properties

3.1 Grouping Effect

Grouping effect refers to the scenario where a group of strongly correlated predictors exhibit small difference in the coefficients, which in turn allows for these predictors to be retained or eliminated from the model together (Zou and Hastie, 2005). Here we first show how the network penalty adjusts for the multicollinearity issues by proving the grouping effect of our estimators (proof can be found in Supplementary Materials). Suppose that the response vector Y for Gaussian models and predictor matrix X have been standardized. We assume that features i and j are linked and only linked to each other and that the sign of estimation is correct. Assume further that the correlation between features i and j is ρ_{ij} and the sign is consistent with the coefficient. We have

$$\left|\left|\hat{\beta}_i\right| - \left|\hat{\beta}_j\right|\right| \leq \frac{\sqrt{2\left(1-|\rho_{ij}|\right)} + \lambda_1 \left|w_i - w_j\right|}{\lambda_2 \left(1+\omega_{ij}\right)}.$$

3.2 Oracle Property

Here we provide the theoretical proof for oracle property, with which a model is considered robust with variable selection and coefficients estimation, on our proposed method (proof can be found in Supplementary Materials). Gaussian and logistic models belong to the exponential family while Cox proportional hazards model does not. Thus the oracle property for Cox model is different from Gaussian and logistic models. Therefore, we proved the oracle property for Cox model and exponential family GLM (not limited to Gaussian and logistic) separately.

3.2.1 Generalized Linear Model in Exponential Family

For generalized linear models in exponential family, such as Gaussian and logistic model, with likelihood function $l\left(Y|X,\theta\right)=h\left(Y\right)\exp\left(Y^{T}\theta-\phi\left(\theta\right)\right)$ where h is a function unrelated to parameters, $\theta=X\beta$ and β is the true coefficient vector. We denote the maximum penalized likelihood estimation as

$$\hat{\beta}^{(n)}=\text{argmax}_{\beta}\left\{\frac{1}{n}\left[Y^{T}X\beta-\phi\left(X\beta\right)\right]-\lambda_{1}^{(n)}\sum_{i=1}^{p}\hat{w}_{i}\left|\beta_{i}\right|-\frac{\lambda_{2}^{(n)}}{2}\beta^{T}L\beta\right\},$$

where the adaptive weight $\hat{w}_i=\frac{1}{|\tilde{\beta}_i|^r}$ where $\tilde{\beta}_i$ is a $\sqrt{n}$-consistent estimator of β_i such as OLS estimate and $r>0$. Let $A_n^*=\left\{i|\hat{\beta}_i^{(n)}\neq 0\right\}$. In our development we mainly consider two special cases:

$$\phi\left(X\beta\right)=\begin{cases}\frac{1}{2}\beta^{T}X^{T}X\beta & \text{Gaussian}\\ \mathbf{1}^{T}\ln\left(\mathbf{1}+\exp\left(X\beta\right)\right), & \text{Logistic}\end{cases}$$

where $\mathbf{1}$ is an $n-$vector of ones. Suppose that $\sqrt{n}\lambda_1^{(n)}\to 0$, $n\lambda_1^{(n)}\to+\infty$, $\sqrt{n}\lambda_2^{(n)}\to 0$ and $\Lambda_{\max}\left(L\right)\leq\lambda_L<+\infty$ where $\Lambda_{\max}\left(\cdot\right)$ represents the largest eigenvalue of a given matrix and λ_L is a constant. We need the following regularity conditions

1. Fisher information matrix $I\left(\beta\right)=E\left[\phi''\left(x\beta\right)X^{T}X\right]$ and $n\lambda_2^{(n)}L$ are finite and positive definite.

2. There exists a sufficient large open set O where $\beta\in O$ and $\forall B\in O$ we have $\left|\phi'''\left(XB\right)\right|\leq M\left(X\right)<+\infty$ and $E\left[M\left(X\right)|x_ix_jx_k\right]<+\infty$ for any $1\leq i,j,k\leq p$,

Let A be the true predictor set, i.e., $A=\{i|\beta_i\neq 0\}$ and β_A is the corresponding coefficient vector. Similarly let $\hat{\beta}_A$ and I_A be the sample estimates and information matrix corresponding to set A. Under the conditions specified above, we have the following conclusions

1. Variable selection consistency: $\lim_n P\left(A_n^* = A\right) = 1$.

2. Asymptotic normality: $\sqrt{n}\left(\hat{\beta}_A^{(n)} - \beta_A\right) \xrightarrow{d} N\left(\mathbf{0}, I_A^{-1}\right)$.

3.2.2 Cox Proportional Hazards Model

The Cox model is not within the exponential family. However, in Cox model there still exists the oracle property as shown by Fan et al. (2002). Denote the counting process and the at-risk process as $N_i(t) = \delta_i I(y_i \leq t)$ and $Y_i(t) = I(y_i \geq t)$ respectively, and the Fisher information matrix as

$$I(\beta) = \int_0^1 v(\beta, t)\, s^{(0)}(\beta, t)\, h_0(t)\, \mathrm{d}t$$

where

$$v(\beta, t) = \frac{s^{(2)}(\beta, t)}{s^{(0)}(\beta, t)} - \left(\frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)}\right)\left(\frac{s^{(1)}(\beta, t)}{s^{(0)}(\beta, t)}\right)^T,$$

$s^{(k)}(\beta, t) = E\left[x(t)^{\otimes k} Y(t) \exp\left(x(t)^T \beta\right)\right]$, $k = 0, 1, 2$ and $h_0(t)$ is the baseline hazards function. Here we assume all the regularity conditions for partial likelihood estimator for Cox model, such as conditions (A-D) in Andersen and Gill (1982a). Let A^C be the complement of set A. Given that $\sqrt{n}\lambda_1^{(n)} \to 0$, $n\lambda_1^{(n)} \to +\infty$, $\sqrt{n}\lambda_2^{(n)} \to 0$ and $\Lambda_{\max}(L) \leq \lambda_L < +\infty$, the proposed estimator $\hat{\beta}^{(n)}$ satisfy the following:

1. Sparsity: $\hat{\beta}_{A^C}^{(n)} = \mathbf{0}$.

2. Asymptotic normality: $\sqrt{n}\left(\hat{\beta}_A^{(n)} - \beta_A\right) \xrightarrow{d} N\left(\mathbf{0}, I_A^{-1}\right)$.

4 Monte Carlo Simulations

We conduct a Monte Carlo study to evaluate the performance of our proposed model. We consider two network structures namely (1) the autoregressive (AR) structure where each feature is connected and only connected to its neighbor, and (2) the HUB structure where the features formed groups with one dominant feature within each group (see Supplementary Materials for the visualization of the network structures).

In our simulation, we generate $p = 200$ features with $n = 500$ samples in which 100 samples are used as training data and the remaining 400 samples are set aside as test data. The features are generated from a multivariate Gaussian distribution with mean zero and variance one. We assign three twenty feature groups with absolute coefficient 0.5, 1 and 2 and random signs for the noninformative features (i.e., those with zero coefficients).

$$\beta = \left(\underbrace{\pm 2, \cdots, \pm 2}_{20}, \underbrace{\pm 1, \cdots, \pm 1}_{20}, \underbrace{\pm 0.5, \cdots, \pm 0.5}_{20}, \underbrace{0, \cdots, 0}_{140} \right)^T$$

For Gaussian model, we generate Gaussian noise with mean zero and standard error $\|\beta\|_2 /2$. For logistic model, we generate the outcome variable from the Bernoulli distribution with probability of the success as the logistic score of the predictors. For Cox model, we generate Weibull baseline hazards with shape parameter 5, scale parameter 2 and censoring time following the uniform distribution $U(2, 15)$ which leads to a censoring rate of approximately 30%.

4.1 Cross Validation (CV) with $p/2$ Constraints

Our estimation method will be referred to as AAG hereafter. We compare our proposed AAG to the elastic net model (implemented in the R package `glmnet`) and network-LASSO

regression without the l_1 adaptive weights (implemented in the R package `glmgraph`). Since `glmgraph` is not implemented for Cox model, we write our own codes for fitting the Cox models for network-LASSO regression without the l_1 adaptive weights. To assess the effect of network misspecification, we consider the scenario where we use (1) the correct network, (2) the incorrect network (AR misspecified as HUB and vice versa), and (3) the estimated network. The sign of network is estimated empirically. We compare this signed network model to our proposed mixture network model that combines (1) a correct network with an incorrect network, (2) a correct network with an estimated network, and (3) an incorrect network with an estimated network. The results of the AR structure as the true network are shown in Tables 1 and 2. The results of HUB structure can be found in the Supplementary Materials. The tuning parameters are chosen via CV with one standard error rule and the number of parameters are constrained to be at most $p/2$.

For Gaussian model, we compare mean absolute error (MAE), mean squared error (MAE), Pearson and Spearman correlation. For logistic model, we compare the area under the receiver operating characteristic curve (AUC) calculated via Robin et al. (2011), accuracy (ACC), Matthews correlation coefficient (MCC) and biserial correlation. For Cox model, we compare the concordance index (C). We report the mean and standard deviations across 100 replicates.

From the simulation results, our proposed method with l_1 adaptive weights yields better performance compared to elastic net `glmnet` and network without l_1 adaptive weights. For both the AR and HUB structures, incorporating the correctly network yields significantly better results compared to the case where network is misspecified as expected. On the other hand, the network mixture approach (i.e., mixing an incorrect network with an estimated data driven network) yields better performance compared to a model with a wrong network

Table 1: Model comparison with AR structure as true network for Gaussian and logistic models. EN is elastic net. Graph is network-LASSO regression without the l_1 adaptive weights. AAG is our proposed method with the l_1 adaptive weights. MixAAG_A_B is our proposed method with the l_1 adaptive weights and a mixture of A and B network. cor,wr, est refer to correct, incorrect and estimated network, respectively.

	Gaussian			
Method	MAE	MSE	Pearson	Spearman
EN	7.283 (0.740)	84.340 (17.447)	0.839 (0.033)	0.824 (0.036)
Graph_cor	6.343 (0.849)	64.578 (22.617)	0.886 (0.049)	0.875 (0.049)
Graph_wr	7.006 (0.682)	77.896 (14.883)	0.859 (0.026)	0.845 (0.028)
Graph_est	6.828 (0.698)	74.217 (15.408)	0.864 (0.028)	0.851 (0.032)
AAG_cor	5.788 (0.543)	53.025 (9.909)	0.896 (0.023)	0.884 (0.026)
AAG_wr	6.685 (0.472)	70.723 (9.827)	0.859 (0.022)	0.846 (0.025)
AAG_est	6.372 (0.525)	64.188 (10.550)	0.873 (0.023)	0.861 (0.026)
MixAAG_cor_wr	5.770 (0.531)	52.756 (9.899)	0.896 (0.022)	0.886 (0.025)
MixAAG_cor_est	5.794 (0.522)	53.180 (9.497)	0.896 (0.021)	0.885 (0.025)
MixAAG_wr_est	6.557 (0.516)	68.010 (10.817)	0.865 (0.024)	0.852 (0.028)
	Logistic			
Method	AUC	ACC	MCC	Biserial
EN	0.839 (0.059)	0.746 (0.049)	0.501 (0.097)	0.716 (0.114)
Graph_cor	0.906 (0.041)	0.812 (0.047)	0.630 (0.090)	0.867 (0.087)
Graph_wr	0.893 (0.031)	0.795 (0.037)	0.599 (0.069)	0.834 (0.063)
Graph_est	0.877 (0.040)	0.777 (0.041)	0.564 (0.077)	0.803 (0.082)
AAG_cor	0.931 (0.024)	0.833 (0.033)	0.676 (0.060)	0.939 (0.054)
AAG_wr	0.889 (0.028)	0.792 (0.031)	0.591 (0.059)	0.839 (0.063)
AAG_est	0.891 (0.031)	0.793 (0.033)	0.596 (0.061)	0.844 (0.071)
MixAAG_cor_wr	0.931 (0.027)	0.834 (0.035)	0.677 (0.066)	0.937 (0.063)
MixAAG_cor_est	0.930 (0.025)	0.831 (0.034)	0.672 (0.061)	0.936 (0.058)
MixAAG_wr_est	0.892 (0.033)	0.791 (0.040)	0.594 (0.072)	0.846 (0.073)

Table 2: Model comparison with AR structure as true network for Cox model. EN is elastic net. Graph is network-LASSO regression without the l_1 adaptive weights. AAG is our proposed method with the l_1 adaptive weights. MixAAG_A_B is our proposed method with the l_1 adaptive weights and a mixture of A and B network. cor,wr, est refer to correct, incorrect and estimated network, respectively.

Cox	
Method	C
EN	0.858 (0.031)
Graph_cor	0.911 (0.022)
Graph_wr	0.876 (0.027)
Graph_est	0.879 (0.027)
AAG_cor	0.931 (0.018)
AAG_wr	0.869 (0.022)
AAG_est	0.900 (0.018)
MixAAG_cor_wr	0.929 (0.019)
MixAAG_cor_est	0.929 (0.018)
MixAAG_wr_est	0.900 (0.019)

or elastic net model.

4.2 Cross validation (CV) vs stability selection (SS)

In practice we constrain the number of selected features to be no more than $p/2$ similar to the default method of R package `glmgraph` to speed up computation. However, this constraint may not be desirable if the true number of informative features is greater than $p/2$. An alternative approach is the stability selection (SS) method as described earlier. In this subsection we compare the variable selection accuracy between cross validation without $p/2$ constraint and the stability selection method. We report the estimated MCC and sensitivity (Sn) for large, medium, and small effect sizes and specificity (Sp) averaged over 100 replications. The results for AR structure are shown in Table 3. The results for HUB structure simulation are provided in Supplementary Materials.

From Table 3, the logistic model with CV without $p/2$ constraint yields lower MCC and Sp compared to the stability selection. For Gaussian and Cox models, CV and SS have comparable performance. The CV approach is also more competitive in computational expense (e.g., for Gaussian model, with 100 samples and 20 features, five fold CV takes 0.05s while 100 replicated SS takes 4.80s).

5 Case Study

5.1 Skin Cutaneous Melanoma Prediction

Skin cutaneous melanoma (SKCM) is an aggressive malignancy that arises from uncontrolled melanocytic proliferation. Gene expression has been shown to be a promising

Table 3: Cross Validation (CV) vs Stability Selection (SS) with AR structure for Gaussian, logistic and Cox models. cor, wr, est refer to correct, incorrect and estimated network, respectively.

Gaussian					
Method	MCC	Sn_large	Sn_medium	Sn_small	Sp
CV_cor_wr	0.637 (0.075)	0.974 (0.045)	0.737 (0.150)	0.364 (0.183)	0.902 (0.138)
CV_cor_est	0.638 (0.082)	0.973 (0.040)	0.748 (0.136)	0.362 (0.161)	0.916 (0.051)
CV_wr_est	0.604 (0.063)	0.926 (0.074)	0.587 (0.142)	0.228 (0.163)	0.936 (0.139)
SS_cor_wr	0.614 (0.066)	0.984 (0.034)	0.804 (0.126)	0.469 (0.186)	0.868 (0.042)
SS_cor_est	0.613 (0.074)	0.982 (0.038)	0.799 (0.136)	0.481 (0.181)	0.867 (0.041)
SS_wr_est	0.597 (0.069)	0.974 (0.042)	0.735 (0.123)	0.359 (0.159)	0.893 (0.044)
Logistic					
Method	MCC	Sn_large	Sn_medium	Sn_small	Sp
CV_cor_wr	0.482 (0.102)	0.976 (0.056)	0.778 (0.212)	0.492 (0.280)	0.718 (0.216)
CV_cor_est	0.482 (0.101)	0.975 (0.048)	0.775 (0.206)	0.498 (0.281)	0.725 (0.200)
CV_wr_est	0.421 (0.081)	0.844 (0.135)	0.443 (0.223)	0.258 (0.196)	0.855 (0.153)
SS_cor_wr	0.536 (0.086)	0.957 (0.054)	0.638 (0.143)	0.319 (0.162)	0.883 (0.030)
SS_cor_est	0.537 (0.083)	0.959 (0.057)	0.643 (0.127)	0.314 (0.156)	0.883 (0.029)
SS_wr_est	0.432 (0.086)	0.895 (0.075)	0.496 (0.128)	0.277 (0.129)	0.860 (0.035)
Cox					
Method	MCC	Sn_large	Sn_medium	Sn_small	Sp
CV_cor_wr	0.705 (0.094)	0.979 (0.034)	0.848 (0.100)	0.539 (0.165)	0.910 (0.062)
CV_cor_est	0.709 (0.089)	0.981 (0.034)	0.847 (0.102)	0.536 (0.168)	0.914 (0.049)
CV_wr_est	0.618 (0.078)	0.946 (0.054)	0.703 (0.134)	0.352 (0.143)	0.916 (0.057)
SS_cor_wr	0.656 (0.077)	0.976 (0.038)	0.862 (0.101)	0.590 (0.167)	0.866 (0.032)
SS_cor_est	0.659 (0.072)	0.979 (0.037)	0.858 (0.103)	0.588 (0.159)	0.868 (0.034)
SS_wr_est	0.583 (0.073)	0.956 (0.045)	0.761 (0.114)	0.427 (0.128)	0.871 (0.027)

biomarker for predicting survival in SKCM (Bittner et al. (2000), Carr et al. (2003) and Mandruzzato et al. (2006)). We apply our proposed method to the Cancer Genome Atlas (TCGA) SKCM gene expression data generated using the RNA-Seq platform. The normalized gene expression values are represented as fragments per kilobase of transcript per million mapped reads upper quartile (FPKM-UQ), downloaded from the UCSC Xena Platform (Goldman et al. (2018)). We define the candidate features as $\log_2(\text{FPKM-UQ} + 1)$. Here, we predict Breslow depth value, metastatic status and overall survival time using Gaussian, Logistic and Cox models, respectively. For each model, we adjust for potential demographic and sample procurement confounding variables. We randomly divide the data into training and test sets (70/30). The network structure is based on cancer subnetwork provided by Huang et al. (2018), combined with an estimated an estimated network in which the signs and strengths are estimated with the method described in Section 2.1 and 2.2. We compare the results between our proposed method and elastic net model.

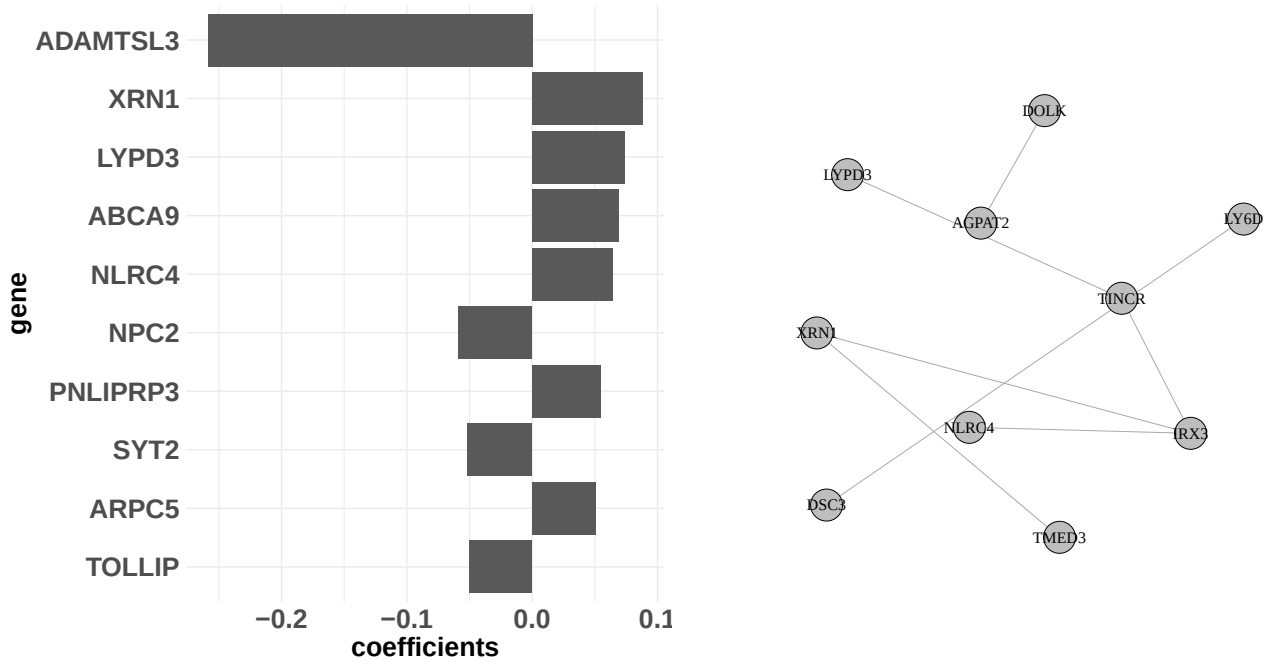
Breslow's depth is an important measurement of tumor thickness and has been incorporated in staging SKCM. We perform a $\log(x + 1)$ transformation on Breslow's depth and use Pearson correlation to prescreen top 1000 candidate features. In Table 4, our proposed model outperforms elastic net method in terms of MAE, MSE, and Pearson correlation, indicating that incorporating a network structure among the genes improves the prediction on Breslow's depth. The results also indicate that the cancer subnetwork of Huang et al. (2018) is sufficient, as mixing this prior network with an estimated network does not yield model improvement. Twenty two genes are in common among the four methods (see the Venn diagram Supplementary Materials). The top 10 genes selected by the AAG model are provided in Figure 1A, whereas the connectivity of the genes are provided in Figure 1B. Frequent mutations of the top most negatively correlated gene with Breslow's depth

Table 4: Comparison results for Breslow's depth analysis

	MAE	MSE	Pearson	Spearman	# Genes
EN	0.581	0.520	0.415	0.423	79
CV_AAG	0.504	0.462	0.533	0.495	23
CV_MixAAG	0.518	0.489	0.527	0.498	47
SS_MixAAG	0.517	0.499	0.492	0.466	140

$ADAMTSL3$ has been found in colorectal cancer (Koo et al., 2007), whereas $GIMAP6$ the top most positively correlated gene is an important immunity-associated gene involved T-cells regulation (Miragaia et al., 2019). Immune system plays an important role in tumor proliferation and tumor-infiltrating lymphocytes (TILs) are manifestation of the host immune response in response to melanoma progression and correlates with Breslow's depth (Taylor et al., 2007). On the other hand, $IRX3$ from the retained network structure (Figure 1B) is implicated in obesity (Schneeberger, 2019), and obesity has been found to be associated with thicker melanoma/higher Breslow's depth (Skowron et al., 2015).

Next, we evaluate the performance of these methods in predicting survival time in melanoma. Altogether, we have 214 patients who died (events), whereas 211 patients have censored time. From Table 5 we can see that our proposed method MixAAG with five fold cross validation gives us the best concordance index (C-Index) gain using gene expression features and the top ten selected features was shown in Table 5. Similar to the results from Breslow's depth analysis, the results indicate that the cancer subnetwork of Huang et al. (2018) is sufficient for this melanoma dataset. The top 10 genes selected by the AAG model are provided in Supplementary Materials. Kaplan Meier curve comparing the risk prediction is provided in Figure 2A, whereas the connectivity of the genes are provided in



(A) (B)

Figure 1: A. Top 10 genes identified from the AAG model. B. Connectivity of the genes in Breslow's depth analysis.

Table 5: Comparison result for survival analysis

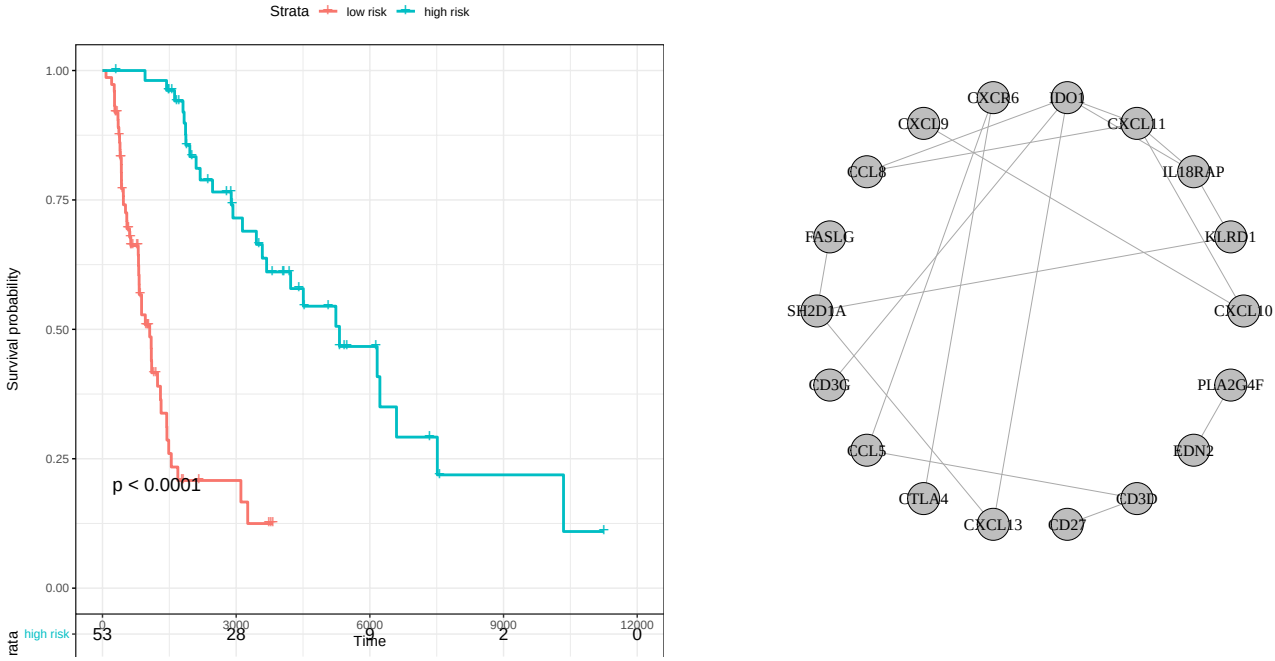
	C-Index	# Genes
CV_EN	0.784	32
CV_AAG	0.795	33
CV_MixAAG	0.770	70
SS_MixAAG	0.750	83

Figure 2B which includes several chemokines and cytokines ($CCL8$, $CXCL10$, $CXCL11$, $CXCL9$, $CXCL13$, $CXCR6$, $CCL5$). Chemokines and cytokines are involved in immune response, and have been found to be important in the recruitment and activation of leukocytes within the microenvironment of skin cancers (Bridge et al., 2018). Thus, the identified network will shed light on how these molecules act as inflammatory mediators of melanoma, which will in turn provide valuable information in the development of immunotherapy.

We also compare the performance of these methods in predicting metastatic from primary melanoma in Supplementary Materials. The results show that all the methods have comparable accuracy in metastatic versus primary melanoma prediction.

6 Conclusion

Incorporating network structure in the prediction model has been shown to be important in high dimensional genomics studies for accurate feature selection and model interpretability. In this paper we propose a mixture network regularized generalized linear model which allows us to combine a prior network and a data driven network. This is particularly useful in the scenarios in which the prior network is not known with certainty. Our model



(A) (B)

Figure 2: A. Kaplan Meier curve from the AAG model prediction. B. Connectivity of the genes in survival analysis.

safeguards against incorporating an incorrect prior network by allowing an optimally mixed network structure in the model.

Our simulation studies shows that the proposed l_1 adapted method yields higher prediction and feature selection accuracy across different scenarios. We also find that cross validation may not be the best approach for feature selection in high dimensional data, especially for binary classification. An alternative strategy is the stability selection method which was shown to yield better performance than cross validation in such scenarios, though it requires a much high computational cost. Based on our simulation results, we suggest using the stability selection method for parameter tuning in binary classification problem, whereas cross validation is often sufficient for Gaussian and Cox models.

An interesting future work include replacing the l_1 penalty with a grouped LASSO penalty to allow for group-wise instead of feature-wise selection. However, the challenge would be to ensure that the group structure inferred from the group LASSO penalty is consistent with the group structure from the data driven network. One possibility is to define the grouped LASSO penalty after obtaining the network mixture within an iterative framework. Another future research is to apply the AAG method to other exponential family, for example, the Poisson and negative binomial regression for modeling count data outcomes. Our proposed model `glmaag` is available on the Comprehensive R Archive Network (CRAN).

SUPPLEMENTARY MATERIALS

Supplementary A: Additional Results on Monte Carlo Simulations

Figure 3 shows the AR and HUB network structures. In HUB structure simulation, we add a uniform noise to the coefficient setting to highlight the dominant variable and avoid the Markov pattern in coefficient space.

$$\beta_{HUB} = \left(\underbrace{\pm 2, \cdots, \pm 2}_{20}, \underbrace{\pm 1, \cdots, \pm 1}_{20}, \underbrace{\pm 0.5, \cdots, \pm 0.5}_{20}, \underbrace{0, \cdots, 0}_{140} \right) + \left(\underbrace{u_1, \cdots, u_{60}}_{60}, \underbrace{0, \cdots, 0}_{140} \right)$$

where u_i follows a uniform distribution.

Simulation results of the HUB structure as the true network for cross validation (CV) with $p/2$ constraints are shown in Tables 6 and 7. For Gaussian model, we compare mean absolute error (MAE), mean squared error (MAE), Pearson and Spearman correlation. For logistic model, we compare the area under the receiver operating characteristic curve (AUC) calculated via Robin et al. (2011), accuracy (ACC), Matthews correlation coefficient (MCC) and biserial correlation. For Cox model, we compare the concordance index (C). We report the mean and standard deviations across 100 replicates. As reported in the main manuscript, our proposed method with l_1 adaptive weights yields better performance compared to elastic net `glmnet` and network without l_1 adaptive weights. For both the AR and HUB structures, incorporating the correctly network yields significantly better results compared to the case where network is misspecified as expected. On the other hand, the network mixture approach (i.e., mixing an incorrect network with an estimated data driven

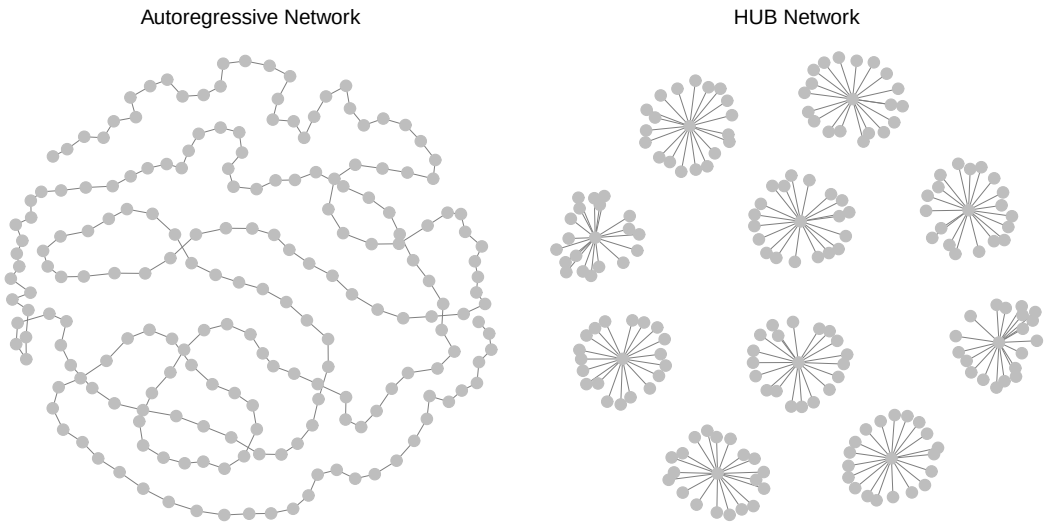


Figure 3: AR and HUB network structures

network) yields better performance compared to a model with a wrong network or elastic net model.

Simulation results comparing variable selection accuracy between cross validation (CV) without $p/2$ constraint and the stability selection (SS) method for HUB structure are shown in Table 8. We report the estimated MCC and sensitivity (Sn) for large, medium, and small effect sizes and specificity (Sp) averaged over 100 replications. From Table 8, CV and SS have comparable performance. The CV approach is also more competitive in computational expense as reported in the main manuscript.

Table 6: Model comparison with HUB structure as true network for Gaussian and logistic models. EN is elastic net. Graph is network-LASSO regression without the l_1 adaptive weights. AAG is our proposed method with the l_1 adaptive weights. MixAAG_A_B is our proposed method with the l_1 adaptive weights and a mixture of A and B network. cor,wr, est refer to correct, incorrect and estimated network, respectively.

	Gaussian			
Method	MAE	MSE	Pearson	Spearman
EN	8.208 (0.959)	107.380 (25.158)	0.609 (0.155)	0.593 (0.157)
Graph_cor	8.106 (0.925)	104.411 (23.276)	0.619 (0.148)	0.603 (0.151)
Graph_wr	7.962 (0.940)	100.699 (23.330)	0.634 (0.148)	0.618 (0.149)
Graph_est	8.218 (0.967)	107.555 (25.384)	0.596 (0.175)	0.580 (0.176)
AAG_cor	7.765 (0.924)	96.130 (23.151)	0.655 (0.104)	0.637 (0.107)
AAG_wr	7.722 (0.836)	94.273 (20.334)	0.661 (0.105)	0.644 (0.109)
AAG_est	7.747 (0.867)	95.101 (21.415)	0.659 (0.103)	0.642 (0.106)
MixAAG_cor_wr	7.729 (0.891)	94.712 (21.631)	0.660 (0.106)	0.643 (0.108)
MixAAG_cor_est	7.770 (0.883)	96.009 (21.734)	0.654 (0.103)	0.637 (0.104)
MixAAG_wr_est	7.691 (0.816)	93.634 (19.626)	0.666 (0.099)	0.649 (0.101)

	Logistic			
Method	AUC	ACC	MCC	Biserial
EN	0.761 (0.093)	0.688 (0.076)	0.383 (0.152)	0.557 (0.193)
Graph_cor	0.772 (0.095)	0.701 (0.075)	0.414 (0.145)	0.596 (0.183)
Graph_wr	0.776 (0.091)	0.700 (0.073)	0.415 (0.133)	0.604 (0.174)
Graph_est	0.761 (0.101)	0.687 (0.079)	0.396 (0.141)	0.583 (0.180)
AAG_cor	0.787 (0.078)	0.711 (0.066)	0.426 (0.131)	0.615 (0.166)
AAG_wr	0.808 (0.067)	0.725 (0.057)	0.456 (0.113)	0.661 (0.145)
AAG_est	0.784 (0.076)	0.707 (0.065)	0.420 (0.128)	0.610 (0.162)
MixAAG_cor_wr	0.804 (0.071)	0.724 (0.061)	0.453 (0.122)	0.656 (0.152)
MixAAG_cor_est	0.786 (0.079)	0.711 (0.069)	0.426 (0.136)	0.615 (0.169)
MixAAG_wr_est	0.804 (0.069)	0.724 (0.059)	0.455 (0.118)	0.656 (0.149)

Table 7: Model comparison with HUB structure as true network for Cox model. EN is elastic net. Graph is network-LASSO regression without the l_1 adaptive weights. AAG is our proposed method with the l_1 adaptive weights. MixAAG_A_B is our proposed method with the l_1 adaptive weights and a mixture of A and B network. cor,wr, est refer to correct, incorrect and estimated network, respectively.

Cox	
Method	C
EN	0.729 (0.088)
Graph_cor	0.730 (0.094)
Graph_wr	0.756 (0.076)
Graph_est	0.725 (0.092)
AAG_cor	0.765 (0.059)
AAG_wr	0.785 (0.054)
AAG_est	0.765 (0.059)
MixAAG_cor_wr	0.780 (0.056)
MixAAG_cor_est	0.763 (0.059)
MixAAG_wr_est	0.781 (0.054)

Table 8: Cross Validation (CV) vs Stability Selection (SS) with HUB structure for Gaussian, logistic and Cox models. cor, wr, est refer to correct, incorrect and estimated network, respectively.

Gaussian					
Method	MCC	Sn_large	Sn_medium	Sn_small	Sp
CV_cor_wr	0.258 (0.081)	0.518 (0.153)	0.315 (0.183)	0.198 (0.164)	0.865 (0.119)
CV_cor_est	0.256 (0.091)	0.498 (0.154)	0.303 (0.179)	0.179 (0.170)	0.871 (0.146)
CV_wr_est	0.260 (0.088)	0.532 (0.162)	0.332 (0.172)	0.218 (0.163)	0.856 (0.120)
SS_cor_wr	0.265 (0.096)	0.545 (0.136)	0.349 (0.130)	0.218 (0.107)	0.864 (0.028)
SS_cor_est	0.271 (0.091)	0.555 (0.126)	0.349 (0.128)	0.224 (0.117)	0.864 (0.029)
SS_wr_est	0.260 (0.092)	0.555 (0.139)	0.340 (0.121)	0.215 (0.097)	0.861 (0.026)
Logistic					
Method	MCC	Sn_large	Sn_medium	Sn_small	Sp
CV_cor_wr	0.247 (0.107)	0.568 (0.221)	0.288 (0.237)	0.225 (0.226)	0.834 (0.167)
CV_cor_est	0.242 (0.083)	0.466 (0.194)	0.223 (0.179)	0.162 (0.149)	0.893 (0.104)
CV_wr_est	0.240 (0.125)	0.586 (0.236)	0.339 (0.277)	0.250 (0.258)	0.790 (0.227)
SS_cor_wr	0.238 (0.111)	0.570 (0.173)	0.294 (0.151)	0.191 (0.118)	0.858 (0.038)
SS_cor_est	0.247 (0.087)	0.620 (0.169)	0.328 (0.132)	0.231 (0.115)	0.835 (0.035)
SS_wr_est	0.243 (0.117)	0.580 (0.171)	0.297 (0.165)	0.189 (0.121)	0.859 (0.036)
Cox					
Method	MCC	Sn_large	Sn_medium	Sn_small	Sp
CV_cor_wr	0.344 (0.083)	0.555 (0.183)	0.279 (0.188)	0.155 (0.137)	0.922 (0.097)
CV_cor_est	0.324 (0.073)	0.474 (0.159)	0.207 (0.156)	0.116 (0.105)	0.951 (0.053)
CV_wr_est	0.341 (0.083)	0.548 (0.188)	0.289 (0.189)	0.169 (0.137)	0.919 (0.084)
SS_cor_wr	0.319 (0.083)	0.645 (0.139)	0.403 (0.138)	0.238 (0.088)	0.862 (0.028)
SS_cor_est	0.306 (0.073)	0.639 (0.124)	0.385 (0.117)	0.244 (0.100)	0.856 (0.033)
SS_wr_est	0.319 (0.088)	0.645 (0.149)	0.405 (0.119)	0.243 (0.099)	0.861 (0.026)

Supplementary B: Mathematical Proofs

Proof of Group Effect

We provide the proof similar to Zou and Hastie (2005), Li and Li (2008), and Yang and Yi (2015).

In our study, we denote the penalized log (partial) likelihood function as

$$Q_n(\beta) = \frac{1}{n}\left[Y^T X\beta - \psi(X\beta, Y)\right] - \lambda_1 \sum_{i=1}^{p} w_i |\beta_i| - \frac{\lambda_2}{2}\beta^T L\beta.$$

Without loss of generality, we set $Y = \Delta$, which is the event indicator vector and

$$\psi(X\beta, Y) = \begin{cases} \frac{1}{2}\beta^T X^T X\beta & \text{Gaussian} \\ \mathbf{1}^T \ln(\mathbf{1} + \exp(X\beta)) & \text{Logistic} \\ Y^T \left(\ln \sum_{j\in R^i} \exp\left(X_j^T \beta\right)\right) & \text{Cox} \end{cases}$$

We take the partial derivative with respect to β_i and β_j and set to zero. Since i and j are only linked to each other, we have

$$\frac{1}{n}x_i^T\left(Y - \psi'\left(X\hat{\beta}, Y\right)\right) - \lambda_1 w_i \text{sgn}\left(\hat{\beta}_i\right) - \frac{\lambda_2}{\sqrt{\xi_i}}\left(\frac{\hat{\beta}_i}{\sqrt{\xi_i}} - \frac{\omega_{ij}\text{sgn}\left(\tilde{\beta}_i\tilde{\beta}_j\right)\hat{\beta}_j}{\sqrt{\xi_j}}\right) = 0$$

$$\frac{1}{n}x_j^T\left(Y - \psi'\left(X\hat{\beta}, Y\right)\right) - \lambda_1 w_j \text{sgn}\left(\hat{\beta}_j\right) - \frac{\lambda_2}{\sqrt{\xi_j}}\left(\frac{\hat{\beta}_j}{\sqrt{\xi_j}} - \frac{\omega_{ij}\text{sgn}\left(\tilde{\beta}_i\tilde{\beta}_j\right)\hat{\beta}_i}{\sqrt{\xi_i}}\right) = 0.$$

Under the assumption $\xi_i = \xi_j = 1$ and $\text{sgn}\left(\tilde{\beta}_i\right) = \text{sgn}(\beta_i)$, we multiply $\text{sgn}\left(\hat{\beta}_i\right)$ to both sides of the first equation, $\text{sgn}\left(\hat{\beta}_j\right)$ to the second equation and obtain

$$\frac{1}{n}\text{sgn}\left(\hat{\beta}_i\right) x_i^T \left(Y - \psi'\left(X\hat{\beta}, Y\right)\right) - \lambda_1 w_i - \lambda_2 \left(\left|\hat{\beta}_i\right| - \omega_{ij}\left|\hat{\beta}_j\right|\right) = 0$$

$$\frac{1}{n}\text{sgn}\left(\hat{\beta}_j\right) x_j^T \left(Y - \psi'\left(X\hat{\beta}, Y\right)\right) - \lambda_1 w_j - \lambda_2 \left(\left|\hat{\beta}_j\right| - \omega_{ij}\left|\hat{\beta}_i\right|\right) = 0.$$

We subtract the first equation from the second and obtain

$$\lambda_2 \left(1 + \omega_{ij}\right)\left(\left|\hat{\beta}_i\right| - \left|\hat{\beta}_j\right|\right)$$

$$= \frac{1}{n}\left(\text{sgn}\left(\hat{\beta}_i\right) x_i^T - \text{sgn}\left(\hat{\beta}_j\right) x_j^T\right)\left(Y - \psi'\left(X\hat{\beta}, Y\right)\right) - \lambda_1 \left(w_i - w_j\right) \tag{5}$$

Since our data has been standardized in the preprocessing step, we have

$$\left(\text{sgn}\left(\hat{\beta}_i\right) x_i^T - \text{sgn}\left(\hat{\beta}_j\right) x_j^T\right)\left(Y - \psi'\left(X\hat{\beta}, Y\right)\right)$$

$$\begin{aligned}
&\leq \frac{1}{n}\left\|\left(\text{sgn}\left(\hat{\beta}_i\right) x_i^T - \text{sgn}\left(\hat{\beta}_j\right) x_j^T\right)\right\|_2 \left\|Y - \psi'\left(X\hat{\beta}, Y\right)\right\|_2 \\
&= \frac{\sqrt{2\left(1 - |\rho_{ij}|\right)}}{n}\left\|Y - \psi'\left(X\hat{\beta}, Y\right)\right\|_2,
\end{aligned}$$

For Gaussian model, $\frac{1}{n}\left\|Y - \psi'\left(X\hat{\beta}, Y\right)\right\|_2 = \frac{1}{n}\left\|Y - X\hat{\beta}\right\|_2 \leq 1$ due to standardization. For logistic model, $\left|y_i - \psi'\left(x_i^T\hat{\beta}\right)\right| = \left|y_i - \left(1 + \exp\left(-x_i^T\hat{\beta}\right)\right)^{-1}\right| \leq 1$. For Cox model, $\left|y_i - \psi'\left(x_i^T\hat{\beta}\right)\right| = \left|\delta_i - \delta_i \exp\left(x_i^T\hat{\beta}\right) / \sum_{j\in R^i} \exp\left(x_j^T\hat{\beta}\right)\right| \leq 1$, so $\left\|Y - \psi'\left(X\hat{\beta}, Y\right)\right\|_2 / n \leq 1$. Therefore,

$$\left(\text{sgn}\left(\hat{\beta}_i\right) x_i^T - \text{sgn}\left(\hat{\beta}_j\right) x_j^T\right)\left(Y - \psi'\left(X\beta, Y\right)\right) \leq \sqrt{2\left(1 - |\rho_{ij}|\right)}.$$

Finally from Equation 5, we have

$$\left|\left|\hat{\beta}_i\right| - \left|\hat{\beta}_j\right|\right| \leq \frac{\sqrt{2\left(1 - |\rho_{ij}|\right)} + \lambda_1 \left|w_i - w_j\right|}{\lambda_2\left(1 + \omega_{ij}\right)}$$

Proof of Oracle Property

Generalized Linear Model in Exponential Family

To prove the oracle property in exponential family, we follow the proof of Zou (2006).

Asymptotic Normality First we prove the asymptotically normality. Let $B = \beta + \frac{u}{\sqrt{n}}$ and u is bounded by a sufficiently large number. Define

$$\Gamma_n(u) = \sum_{i=1}^{n} \left(-y_i \left(x_i^T \left(\beta + \frac{u}{\sqrt{n}} \right) \right) + \phi \left(x_i^T \left(\beta + \frac{u}{\sqrt{n}} \right) \right) \right)$$

$$+ n\lambda_1^{(n)} \sum_{i=1}^{p} \hat{w}_i \left| \beta_i + \frac{u_i}{\sqrt{n}} \right| + \frac{n\lambda_2^{(n)}}{2} \left(\beta + \frac{u}{\sqrt{n}} \right)^T L \left(\beta + \frac{u}{\sqrt{n}} \right).$$

Let $\hat{u}^{(n)} = \arg\min_u \Gamma_n(u)$, we have $\hat{u}^{(n)} = \sqrt{n}\left(\beta^{(n)} - \beta\right)$. By Taylor expansion we have $\Gamma_n(u) - \Gamma_n(0) = H^{(n)}(u)$, where

$$H^{(n)}(u) \equiv A_1^{(n)} + A_2^{(n)} + A_3^{(n)} + A_4^{(n)}$$

with

$$A_1^{(n)} = -\sum_{i=1}^{n} \left(y_i - \phi'\left(x_i^T \beta \right) \right) \frac{x_i^T u}{\sqrt{n}}$$

$$A_2^{(n)} = \frac{1}{2} \sum_{i=1}^{n} \phi''\left(x_i^T \beta \right) u^T \frac{x_i x_i^T}{n} u + \lambda_2^{(n)} u^T L u$$

$$A_3^{(n)} = \sqrt{n}\lambda_1^{(n)} \sum_{i=1}^{p} \hat{w}_i \sqrt{n} \left(\left| \beta_i + \frac{u_i}{\sqrt{n}} \right| - |\beta_i| \right)$$

$$A_4^{(n)} = n\lambda_2^{(n)} \beta^T L \frac{u}{\sqrt{n}}$$

and

$$A_5^{(n)} = \frac{n^{-\frac{3}{2}}}{6} \sum_{i=1}^{n} \phi^{'''} \left(x_i^T \underline{\beta}\right) \left(x_i^T u\right)^3$$

Using the property of exponential family, we have

$$E_{y_i,x_i} \left[\left(y_i - \phi^{'} \left(x_i^T \beta\right) \right) x_i^T u \right] = 0$$

and

$$\text{var} \left(\left(y_i - \phi^{'} \left(x_i^T \beta\right) \right) x_i^T u \right) = E_{x_i} \left[\phi^{''} \left(x_i^T \beta\right) \left(x_i^T u\right)^2 \right] = u^T I\left(\beta\right) u.$$

Therefore, using Central Limit theorem we have $A_1^{(n)} \xrightarrow{d} u^T N\left(\mathbf{0}, I\left(\beta\right)\right)$. For the second term, since $\sum_{i=1}^{n} \phi^{''} \left(x_i^T \beta\right) \frac{x_i x_i^T}{n} \xrightarrow{p} I\left(\beta\right)$, $\lambda_2^{(n)} u^T L u \to 0$, we have $A_2^{(n)} \xrightarrow{p} \frac{1}{2} u^T I\left(\beta\right)^{-1} u$. It is obvious that

$$\sqrt{n} \lambda_1^{(n)} \hat{w}_i \sqrt{n} \left(\left| \beta_i + \frac{u_i}{\sqrt{n}} \right| - \left|\beta_i\right| \right) \xrightarrow{p} \begin{cases} 0 & \beta_i \neq 0 \\ 0 & \beta_i = 0 \ and \ u_i = 0 \\ +\infty & \beta_i = 0 \ and \ u_i \neq 0 \end{cases}$$

Based on our assumptions defined in Section 3.2.1 of the main manuscript, we have

$$A_4^{(n)} \to 0$$

By the regularity condition 2 (see Section 3.2.1 of the main manuscript), $A_5^{(n)}$ is bounded by

$$6\sqrt{n} A_5^{(n)} \leq \frac{1}{n} \sum_{i=1}^{n} M\left(x_i^T\right) \left|x_i^T u\right|^3 \xrightarrow{p} E\left[M\left(x\right) \left|x^T u\right|^3 \right] < +\infty.$$

Thus, according to Slutsky's theorem we have $H^{(n)}\left(u\right) \xrightarrow{d} H\left(u\right)$ for every u where

$$H\left(u\right) = \begin{cases} \frac{1}{2} u^T I\left(\beta\right)^{-1} u - u_A^T W_A & u_i = 0 \ \forall i \notin A \\ +\infty & \text{else} \end{cases}$$

where $W = N(\mathbf{0}, I(\beta))$. $H^{(n)}$ is convex with unique minimum $\left((I_A)^{-1} W_A, 0\right)^T$. Finally we have

$$\hat{u}_A^{(n)} \xrightarrow{d} I_A^{-1} W_A \text{ and } \hat{u}_{A^C}^{(n)} \xrightarrow{d} \mathbf{0}. \tag{6}$$

Since $W_A = N(\mathbf{0}, I_A)$, this proves the asymptotic normality.

Variable Selection Consistency $\forall i \in A$, the asymptotic property indicates that $P(i \in A_n^*) \to 1$. Therefore, it is sufficient to show that $\forall j \notin A$, $P(j \in A_n^*) \to 0$. For the case $j \in A_n^*$, by KKT optimality conditions we need

$$\sum_{i=1}^{n} x_{ij} \left(y_i - \phi'\left(x_i^T \hat{\beta}^{(n)}\right)\right) - n\lambda_2^{(n)} \sum_{i=1}^{p} l_{ij} \hat{\beta}_j^{(n)} = n\lambda_1^{(n)} \hat{w}_j$$

thus $P(j \in A_n^*) \leq P\left(\sum_{i=1}^{n} x_{ij} \left(y_i - \phi'\left(x_i^T \hat{\beta}^{(n)}\right)\right) - n\lambda_2^{(n)} \sum_{i=1}^{p} l_{ij} \hat{\beta}_j = n\lambda_1^{(n)} \hat{w}_j\right)$. Note that

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} x_{ij} \left(y_i - \phi'\left(x_i^T \hat{\beta}^{(n)}\right)\right) - \sqrt{n}\lambda_2^{(n)} \sum_{i=1}^{p} l_{ij} \hat{\beta}_j^{(n)} = B_1^{(n)} + B_2^{(n)} + B_3^{(n)},$$

where

$$B_1^{(n)} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} x_{ij} \left(y_i - \phi'\left(x_i^T \hat{\beta}\right)\right)$$

$$B_2^{(n)} = \left(\frac{1}{n} \sum_{i=1}^{n} x_{ij} \phi''\left(x_i^T \hat{\beta}\right) x_i^T\right) \sqrt{n}\left(\beta - \hat{\beta}^{(n)}\right)$$

$$B_3^{(n)} = \frac{1}{n} \sum_{i=1}^{n} x_{ij} \phi'''\left(x_i^T \tilde{\beta}_*\right) \left(x_i^T \sqrt{n}\left(\beta - \hat{\beta}^{(n)}\right)\right)^2 / \sqrt{n}$$

and

$$B_4^{(n)} = -\sqrt{n}\lambda_2^{(n)} L\hat{\beta}^{(n)}$$

where β_* is between $\hat{\beta}^{(n)}$ and β. By the previous proof and Equation 6, we know that $B_1^{(n)} \xrightarrow{d} N(\mathbf{0}, I(\beta))$. Since $\frac{1}{n}\sum_{i=1}^n x_{ij}\phi''\left(x_i^T\hat{\beta}\right)x_i^T \xrightarrow{p} I_i$, $B_2^{(n)}$ converges to a normal random variable. From regularity condition 2 and Equation 6, we have $B_3^{(n)} = O_p\left(\frac{1}{\sqrt{n}}\right)$. Using our assumption defined earlier, we have $B_4^{(n)} \xrightarrow{p} \mathbf{0}$. Meanwhile

$$\frac{n\lambda_1^{(n)}\hat{w}_j}{\sqrt{n}} = \frac{n\lambda_1^{(n)}}{\sqrt{n}} n^{\frac{1}{2}} \frac{1}{\left|\sqrt{n}\hat{\beta}_j\right|} \xrightarrow{p} +\infty$$

Therefore, $P(j \in A_n^*) \to 0$. This proves the oracle property for generalized linear models with exponential family.

Cox's Proportional Hazards Model

To prove this property, we follow the proof given in Zhang and Lu (2007).

l_2 Error Bound First we prove the lemma that if $\sqrt{n}\lambda_1^{(n)} = O_p(1)$, the AAG estimator satisfies $\left\|\hat{\beta}^{(n)} - \beta\right\| = O_p(\sqrt{n})$.

The log partial likelihood $l(\beta)$ can be written as

$$l(\beta) = \sum_{i=1}^n \int_0^1 x_i(s)^T \beta \mathrm{d}N_i(s) - \int_0^1 \ln\left(\sum_{i=1}^n Y_i(s)\exp\left(x_i(s)^T\beta\right)\right)\mathrm{d}\bar{N}(s) \tag{7}$$

where $N_i(t)$ is the counting process $\overline{N} = \sum_{i=1}^n N_i$. By Andersen and Gill (1982b)'s proof, there exists a neighbood of β that $\forall B$ in the neighborhood, we have

$$\frac{1}{n}\left[l_n(B) - l_n(\beta)\right] = \int_0^1 \left((B-\beta)^T s^{(1)}(\beta,t) - s^{(0)}(\beta,t)\ln\frac{s^{(0)}(B,t)}{s^{(0)}(\beta,t)}\right)h_0(t)\,\mathrm{d}t$$

$$+O_p\left(\frac{\|B-\beta\|_2}{\sqrt{n}}\right).$$

Consider a C-ball $B_n(C)=\left\{B|B=\beta+n^{-1/2}u,\|u\|_2\leq C,C>0\right\}$ with boundary $\partial B_n(C)$. Denote the penalized log partial likelihood function as

$$Q_n(\beta)=l_n(\beta)-n\lambda_1^{(n)}\sum_{i=1}^{p}\frac{|\beta_i|}{\left|\tilde{\beta}_i\right|}-\frac{n\lambda_2^{(n)}}{2}\beta^T L\beta$$

When n is large, $Q_n(\beta)$ is strictly convex. Therefore, there is a unique maximizer $\hat{\beta}_n$ of $Q_n(\beta)$ for large n. It is sufficient to show that, $\forall\epsilon>0$, there exists a large constant C such that

$$P\left(\sup_{B\in\partial B_n(C)}Q_n(B)<Q_n(\beta)\right)\geq 1-\epsilon \tag{8}$$

This shows that with probability of at least $1-\epsilon$, there exists a local maximizer of $Q_n(\beta)$ in $B_n(C)$, thus $\hat{\beta}_n$ must satisfy $\left\|\hat{\beta}^{(n)}-\beta\right\|=O_p\left(n^{-1/2}\right)$. Furthermore, we have $n^{-1/2}s_n(\beta)=O_p(1)$ and $n^{-1}\nabla s_n(\beta)=I(\beta)+o_p(1)$. For $\forall B\in\partial B_n(C)$, by the second-order Taylor expansion of log partial likelihood function we have

$$\begin{aligned}\frac{1}{n}\left(l_n\left(\beta+\frac{u}{\sqrt{n}}\right)-l_n(\beta)\right)&=\frac{1}{n}s_n^T(\beta)\frac{u}{\sqrt{n}}-\frac{1}{2n}u^T\frac{\nabla s_n(\beta)}{n}u+\frac{1}{n}u^T o_p(1)u\\&=-\frac{1}{2n}u^T\left(I(\beta)+o_p(1)\right)u+\frac{1}{n}O_p(1)\sum_{i=1}^{p}|u_i|.\end{aligned}$$

We have

$$
\begin{aligned}
D_n(u) &\equiv \frac{1}{n}\left[Q_n\left(\beta+\frac{u}{\sqrt{n}}\right)-Q_n(\beta)\right] \\
&= \frac{1}{n}\left[l_n\left(\beta+\frac{u}{\sqrt{n}}\right)-l_n(\beta)\right]-\lambda_1^{(n)}\sum_{i=1}^{p}\left(\frac{\left|\beta_i+\frac{u_i}{\sqrt{n}}\right|}{|\tilde{\beta}_i|}-\frac{|\beta_i|}{|\tilde{\beta}_i|}\right) \\
&- \frac{\lambda_2^{(n)}}{2}\left(\left\|\beta+\frac{u}{\sqrt{n}}\right\|_L^2-\|\beta\|_L^2\right) \\
&\leq \frac{1}{n}\left[l_n\left(\beta+\frac{u}{\sqrt{n}}\right)-l_n(\beta)\right]-\lambda_1^{(n)}\sum_{i\in A}\left(\frac{\left|\beta_i+\frac{u_i}{\sqrt{n}}\right|}{|\tilde{\beta}_i|}-\frac{|\beta_i|}{|\tilde{\beta}_i|}\right) \\
&- \frac{\lambda_2^{(n)}}{2}\left(\left\|\beta_A+\frac{u_A}{\sqrt{n}}\right\|_{L_A}^2-\|\beta_A\|_{L_A}^2\right)
\end{aligned}
$$

$$
\leq \frac{1}{2n}u^T\left(I(\beta)+o_p(1)\right)u+\frac{1}{n}O_p(1)\sum_{i\in A}|u_i|+n^{-1/2}\lambda_1^{(n)}\sum_{i\in A}\frac{|u_i|}{|\tilde{\beta}_i|} \tag{9}
$$

$$
+n^{-1/2}\lambda_2^{(n)}\sqrt{\beta_A^T L_A u_A} \tag{10}
$$

Since $\left\|\tilde{\beta}-\beta\right\|_2 = O_p\left(n^{-1/2}\right)$, we have for $i\in A$,

$$
\frac{1}{|\tilde{\beta}_i|}=\frac{1}{|\beta_i|}-\frac{\operatorname{sgn}(\beta_i)}{\beta_i^2}\left(\tilde{\beta}_i-\beta_i\right)+o_p\left(\left|\tilde{\beta}_i-\beta_i\right|\right)=\frac{1}{|\beta_i|}+\frac{O_p(1)}{\sqrt{n}}.
$$

Moreover, $\sqrt{n}\lambda_1^{(n)}=O_p(1)$ we have

$$
\begin{aligned}
\frac{1}{\sqrt{n}}\lambda_1^{(n)}\sum_{i\in A}\frac{|u_i|}{|\tilde{\beta}_i|} &= \frac{1}{\sqrt{n}}\lambda_1^{(n)}\sum_{i\in A}\left(\frac{|u_i|}{|\beta_i|}+\frac{|u_i|}{\sqrt{n}}O_p(1)\right) \\
&\leq Cn^{-1/2}\lambda_n O_p(1) \\
&= Cn^{-1}\left(\sqrt{n}\lambda_1^{(n)}\right)O_p(1) \\
&= Cn^{-1}O_p(1)
\end{aligned}
$$

Similarly, using $\sqrt{n}\lambda_2^{(n)} = O_p(1)$ we have $n^{-1/2}\lambda_2^{(n)}\sqrt{\beta_A^T L_A u_A} \leq C^{1/2}n^{-1}O_p(1)$. In 10, the first term is of order $C^2 n^{-1}$, therefore we can choose a sufficiently large C to make 10 dominated by the first term. Thus, 8 holds and the proof is complete.

Sparsity To show $\hat{\beta}_{A^C} = \mathbf{0}$, it is sufficient to show that $\forall B_A$, $\|B_A - \beta_A\| = O_p\left(n^{-1/2}\right)$ and $\forall C$

$$Q_n(B, 0) = \max_{\|B_2\| \leq Cn^{-1/2}} Q_n(B_A, B_{A^C}).$$

We show that with probability tending to one, $\forall B_A$ satisfying $\|B_A - \beta_A\| = O_p\left(n^{-1/2}\right)$, $\partial Q(B)/\partial B_i$ and B_i have different signs for $B_i \in \left(-Cn^{-1/2}, Cn^{-1/2}\right)$ where $i \in A^C$. For each B in a neighborhood of β, by Taylor expansion of 7,

$$l_n(B) = l_n(\beta) + nf(B) + O_p\left(\sqrt{n}\|B - \beta\|\right)$$

where $f(B) = -\frac{1}{2}(B-\beta)^T (I(\beta) + o(1))(B - \beta)$. For $i \in A^C$, we have

$$\begin{aligned}\frac{\partial Q_n(B)}{\partial B_i} &= \frac{\partial l_n(B)}{\partial B_i} - n\lambda_1^{(n)}\frac{\operatorname{sgn}(B_j)}{|\tilde{\beta}_i|} - n\lambda_2^{(n)}L_i B \\ &= O_p\left(n1^{1/2}\right) - \left(n\lambda_1^{(n)}\right)n^{1/2}\frac{\operatorname{sgn}(B_i)}{\left|n^{1/2}\tilde{B}_i\right|} - \sqrt{n}\lambda_2^{(n)}L_i\sqrt{n}B.\end{aligned}$$

Note that $|\sqrt{n}B_i| < C$, $\sqrt{n}\lambda_2^{(n)} = O_p(1) \Rightarrow n^{1/2}\lambda_2^{(n)}L_i\sqrt{n}B = CO_p(1)$. Since $\sqrt{n}\left(\tilde{\beta}_i - 0\right) = O_p(1)$, we have

$$\partial Q_n(B)/\partial B_i = n^{1/2}\left[O_p(1) - n\lambda_1^{(n)}\operatorname{sgn}(B_i)/|O_p(1)|\right]$$

Since $n\lambda_1^{(n)} \to +\infty$, the sign of $\partial Q_n(B)/\partial B_i$ is determined by $\operatorname{sgn}(B_i)$ when n is sufficiently large, so they always have different signs.

Asymptotic Normality From the l_2 error bound, it is obvious that there exists a root-n consistent maximizer $\hat{\beta}_A^{(n)}$ of $Q_n(B_A, \mathbf{0})$, i.e.

$$\left.\frac{\partial Q_n(B)}{\partial B_A}\right|_{B=\left\{\hat{\beta}_{A,n}^{(n)T}, \mathbf{0}^T\right\}^T} = 0.$$

Let $s_{A,n}(B)$ be the true predictor elements of $s_n(B)$ and $\hat{I}_A(B)$ be the true predictor submatrix of $\nabla s_n(B)$, we have

$$\begin{aligned}
0 &= \left.\frac{\partial Q_n(B)}{\partial B_A}\right|_{B=\left\{\hat{\beta}_{A,n}^{(n)T}, \mathbf{0}^T\right\}^T} \\
&= \left.\frac{\partial l_n(B)}{\partial B_1}\right|_{B=\left\{\hat{\beta}_{A,n}^{(n)T}, \mathbf{0}^T\right\}^T} - n\lambda_1^{(n)} \frac{\operatorname{sgn}\left(\hat{\beta}_A\right)}{\tilde{\beta}_A} - n\lambda_2 LB \\
&= s_{A,n}(\beta) - \hat{I}_{11}(\beta^*)\left(\hat{\beta}_A^{(n)} - \beta_A\right) - n\lambda_1^{(n)} \frac{\operatorname{sgn}(\beta_A)}{\tilde{\beta}_A} - n\lambda_2 LB
\end{aligned}$$

where β^* is between $\hat{\beta}^{(n)}$ and β. We obtained the last equation by $\operatorname{sgn}\left(\hat{\beta}_A\right) = \frac{\operatorname{sgn}(\beta_A)}{\tilde{\beta}_A}$ when n is sufficiently large since it is a root-n consistent estimator. By Andersen and Gill (1982b), $s_{A,n}(\beta)/\sqrt{n} \xrightarrow{d} N(\mathbf{0}, I_A(\beta_A))$ and $\hat{I}_A(\beta^*)/n \xrightarrow{p} I_A(\beta_A)$. Furthermore, if $\sqrt{n}\lambda_1^{(n)} \to 0$, $\sqrt{n}\lambda_2^{(n)} \to 0$, $\Lambda_{\max}(L) \leq M < +\infty$, we have

$$\sqrt{n}\left(\hat{\beta}_A^{(n)} - \beta_A\right) = I_A^{-1}(\beta_A)\, n^{-\frac{1}{2}} s_{A,n}(\beta) + o_p(1).$$

Therefore, by Slutsky's Theorem, $\sqrt{n}\left(\hat{\beta}_A^{(n)} - \beta_A\right) \xrightarrow{d} N\left(\mathbf{0}, I_A^{-1}\right)$.

Supplementary C: Additional Results on Skin Cutaneous Melanoma Prediction

Figure 4 compares the overlap between the genes retained by the different methods in Breslow's depth analysis. Twenty two genes are in common among the four methods.

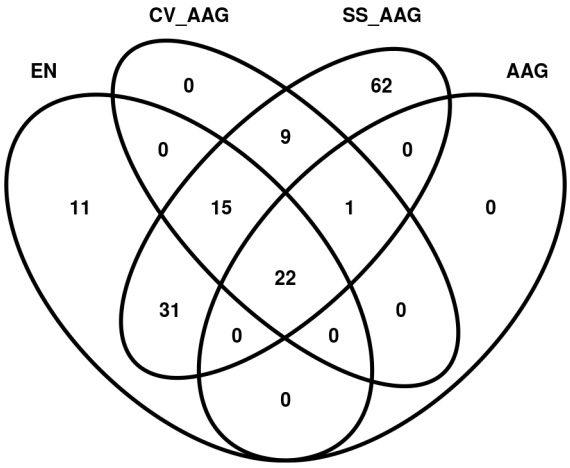
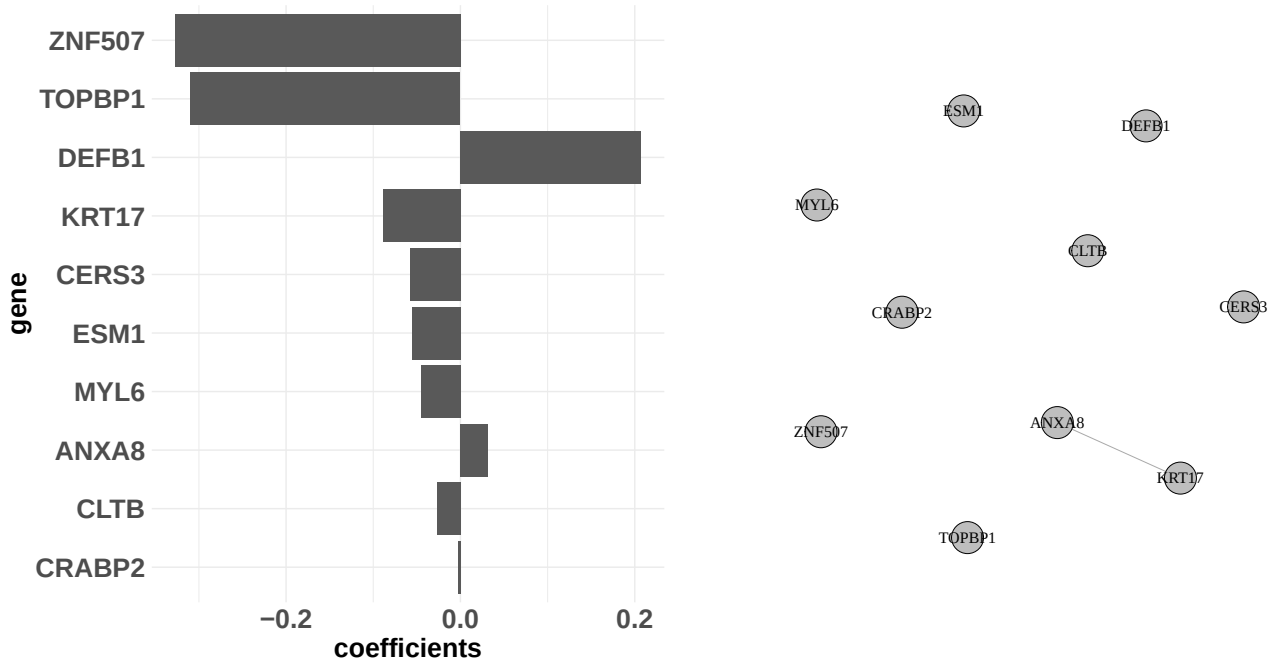


Figure 4: Venn diagram comparing the overlap in the selected genes for Breslow's depth analysis

Table 9 compares the performance of the different methods, which shows that all the methods have comparable accuracy in metastatic versus primary melanoma prediction, however the stability selection method retains a large number of genes in the model. The top 10 genes selected by the MixAAG model are provided in Figure 5A, whereas the connectivity of the genes are provided in Figure 5B.

Table 9: Comparison result for metastatic vs primary prediction

	AUC	ACC	MCC	J	# Genes
CV_EN	0.992	0.976	0.931	0.971	8
CV_AAG	0.993	0.976	0.931	0.971	16
CV_MixAAG	0.994	0.976	0.931	0.971	10
SS_MixAAG	0.990	0.944	0.829	0.841	109



(A) (B)

Figure 5: A. Top 10 genes identified from the MixAAG model. B. Connectivity of the genes in metastatic vs primary melanoma prediction analysis.

The top 10 genes selected by the AAG model for survival analysis are provided in Figure 6.

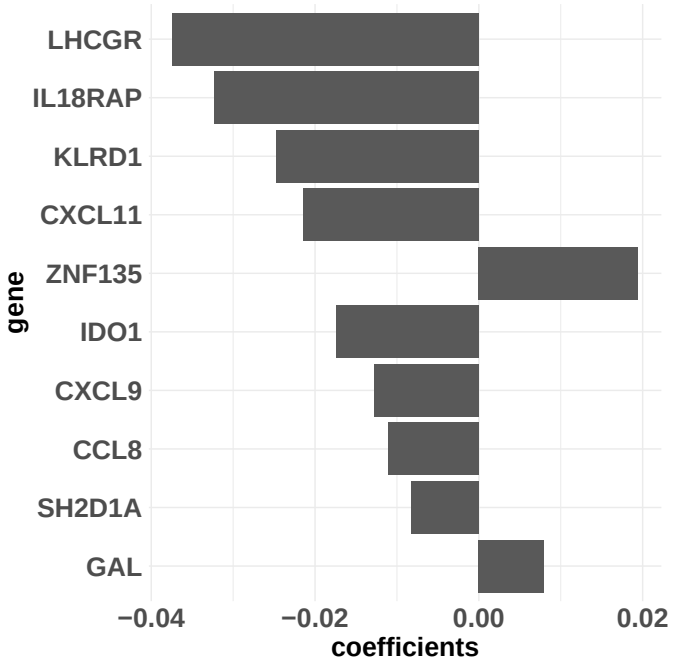


Figure 6: Top 10 genes identified from the AAG model in survival analysis

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