Genetics and population analysis

**Precision Lasso: accounting for correlations and linear dependencies in high-dimensional genomic data**

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**Abstract**

**Motivation:** Association studies to discover links between genetic markers and phenotypes are central to bioinformatics. Methods of regularized regression, such as variants of the Lasso, are popular for this task. Despite the good predictive performance of these methods in the average case, they suffer from _unstable_ selections of correlated variables and _inconsistent_ selections of linearly dependent variables. Unfortunately, as we demonstrate empirically, such problematic situations of correlated and linearly dependent variables often exist in genomic datasets and lead to under-performance of classical methods of variable selection.

**Results:** To address these challenges, we propose the Precision Lasso. Precision Lasso is a Lasso variant that promotes sparse variable selection by regularization governed by the covariance and inverse covariance matrices of explanatory variables. We illustrate its capacity for _stable_ and _consistent_ variable selection in simulated data with highly correlated and linearly dependent variables. We then demonstrate the effectiveness of the Precision Lasso to select meaningful variables from transcriptomic profiles of breast cancer patients. Our results indicate that in settings with correlated and linearly dependent variables, the Precision Lasso outperforms popular methods of variable selection such as the Lasso, the Elastic Net and Minimax Concave Penalty (MCP) regression.

**Availability and implementation:** Software is available at https://github.com/HaohanWang/thePrecisionLasso.

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**Supplementary information:** Supplementary data are available at Bioinformatics online.

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1 Introduction

High-throughput technology for profiling gene expression levels and assaying genetic variations at a genome-wide scale produces massive data, creating an opportunity to study the genetic causes of complex diseases by statistical methods. Computationally screening for putatively causal genes is a key step in hypothesis generation, and many such techniques have been proposed. These can be categorized into several generations, starting with hypothesis testing (Posada and Crandall, 1998). Unfortunately, traditional hypothesis testing methods are limited to independently considering associations for each biomarker. This is a major limitation of the approach since epistatic effects remove the assumed independence between explanatory variables.

To jointly consider associations between all biomarkers and a phenotype, linear regression-based methods (Ogutu et al., 2012) have become more popular. Although ordinary least squares...
regression can consider multiple genes simultaneously, it assigns non-zero effect sizes to all explanatory variables and fails when there are more genes than samples under consideration, the high-dimensional regime that is common in genomic applications. To solve this problem, regularization via the Lasso (Tibshirani, 1996) is often used to reduce the selected set of explanatory variables. Given a design matrix X (of size $n \times p$, with $X_j$ the jth variable of the rth sample) and dependent variable $Y$ (of size $n \times 1$), the Lasso solves the problem

$$\arg\min_{\beta} \frac{1}{2} \|Y - X\beta\|_2^2 \text{ subject to } \|\beta\|_1 \leq t$$

where $\beta$ represents the effect sizes of the explanatory variables and $t > 0$ controls the amount of regularization. With the $l_1$-norm as a constraint, the Lasso learns a set of sparse coefficients $\beta$ that indicates the most relevant explanatory variables. However, the Lasso has several drawbacks for structured data; here, we describe two situations that lead to undesirable properties in sparse variable selection: correlation and linear dependence between explanatory variables.

First, if two explanatory variables are highly correlated and effect sizes are unconstrained, then the explanatory variables show very similar influence on the response variable. In such a situation, the Lasso will only select one variable at random (Xu et al., 2012). This is problematic when the results are used for hypothesis generation because we would like to simultaneously select all variables which have the same evidence of activity. Here, we refer to this property as instability.

Second, the Lasso struggles when explanatory variables are linearly dependent. Given explanatory variables $X_i, X_j, X_k$ with effect sizes $\beta_i, \beta_j, \beta_k$, if $X_i = aX_j + cX_k$ and $a\beta_i \geq 0$ and $c\beta_k \geq 0$, then the Lasso is guaranteed to select the combined variable $X_k$ when $ac > 0$ (Zhao and Yu, 2006). This is undesirable when $X_i, X_j$ are better experimental targets; for instance, $X_i$ and $X_j$ may be somatic mutations and $X_k$ a protein expression level. Here, we refer to this property as the inconsistency of the Lasso, following the convention of previous work (Zhao and Yu, 2006). Although linear dependence may involve arbitrarily many variables (and this is indeed an issue in practice), in the special case of two variables, linearly dependent variables may also be understood as the limiting case of perfect correlation.

Until now, these two properties have not been addressed simultaneously in a satisfactory manner. Unfortunately, as we will show, these two properties are common in genomic datasets and degrade performance in inference tasks such as the detection of putatively causal mutations. In this paper, we aim to address these two properties by introducing a new variable selection method called the Precision Lasso. We demonstrate empirically that our proposed model can mitigate the instability and inconsistency properties discussed here.

The main contributions of this paper are 3-fold:

i. We demonstrate that real-world genomic datasets contain highly correlated and linearly dependent variables, raising concerns about instability and inconsistency for existing variable selection methods.

ii. We illustrate through experiments that these two properties degrade the performance of traditional variable selection methods.

iii. We propose a novel penalization to handle these properties and show that it outperforms traditional methods on simulated data and real breast cancer transcriptomic data.

1.1 Related work

It is well-known that the $l_0$-norm regularizer is optimal in variable selection, however, it leads to a non-convex programme which is NP-hard (Barron et al., 1999; Davis et al., 1997; Manyem and Ugon, 2012). To overcome this difficulty, $l_1$-norm regularization was proposed by Tibshirani (1996) as a tractable convex relaxation to $l_0$-regularization. Despite its many attractive properties (e.g. good predictive power), $l_1$-regularization—or Lasso regression—still suffers from the unstable and inconsistency properties mentioned in the previous section. The adaptive Lasso (Zou, 2006) aims to remedy some of the issues with vanilla $l_1$-regularization. This method re-weights the Lasso penalty for each variable based on the variable’s contribution in unregularized linear regression, and leads to more favourable variable selection properties. Unfortunately, the adaptive Lasso has also been shown to perform poorly in the presence of highly correlated variables (Krämer et al., 2009).

Another popular alternative is $l_2$-norm regularization, often called ridge regression or Tikhonov regularization (Golub et al., 1999; Hoerl and Kennard, 1970), however, this strategy loses the attractive variable selection properties of the Lasso. There are also some works that aim to combine the advantages of $l_1$- and $l_2$-regularization, such as the elastic net (Zou and Hastie, 2005) and the trace Lasso (Grave et al., 2011). These two approaches are designed to handle correlated variables, but they have no guarantees for linearly dependent variables. In other words, these methods can select variables stably, but not consistently. We also mention the non-negative Garrote (Yuan and Lin, 2007); however, this is only applicable when $p < n$ and therefore is not applicable to most tasks in bioinformatics.

Another approach to overcome these difficulties is to use non-convex regularizers, introduced by Fan and Li (2001). Examples include the Smoothly Clipped Absolute Deviation (SCAD) (Fan and Li, 2001) and the Minimax Concave Penalty (MCP) (Zhang, 2010). These non-convex regularizers are designed to overcome the problems inherent with the Lasso, and have the desirable properties of unbiasedness, continuity and sparsity. A recent review of these methods can be found in (Zhang and Zhang, 2012). While these variable selection methods are promising compared to the Lasso, we will show that they also inherit many of the Lasso’s problems in practice.

In addition to these general purpose algorithms, additional methods tailored specifically for GWAS have been developed. To tackle the high-dimensionality of genomic datasets, Wu et al. (2009) reduced the dimension of SNPs via a simple score criterion, then applied the LASSO to the reduced set. He and Lin (2011) extended this approach based on Fan and Lv (2008) with a more sophisticated score criterion where the score is conditioned on SNPs that were selected previously. Bayesian variable selection methods (Guan and Stephens, 2011; Peltola et al., 2012) have also enjoyed recent popularity for selecting SNPs in GWAS. Unfortunately, none of these methods explicitly address the problems raised by inconsistent selection.

1.2 Motivation

Gene expression profiles can result in unstable variable selection. As expression levels of genes within a regulatory pathway are highly correlated (Michalopoulos et al., 2012), the Lasso will be unstable for selection of variables when several of the variables participate in the same regulatory pathway. This can lead researchers to believe that a single element of the pathway is likely to be causal for a
phenotype (based on variable selection), when in reality the evidence is shared between all elements of the pathway.

The existence of expression profiles that lead to inconsistent behaviour, however, has not been convincingly demonstrated previously. Here, we verify that real gene expression profiles indeed exhibit linear dependencies, thereby introduce the problem of inconsistency.

To show this, we must first formalize the definition of inconsistency. We call an explanatory variable an active variable if the explanatory variable encodes an interaction that influences the value of the response variable. In a linear regression model for these variables, this means that the coefficient for this variable is non-zero. For the Lasso to select consistently, data must satisfy the irrepresentable condition (Ravikumar et al., 2010; Zhao and Yu, 2006), which states that the association between the active variables and the non-active variables cannot be too strong. Formally, the irrepresentable condition states that

\[ |(X^{(2)})^T X^{(1)} ((X^{(1)})^T X^{(1)})^{-1} \text{sign}(\beta^{(1)})| < 1 - \eta, \]

where \( X^{(1)} \) is the set of active variables, \( X^{(2)} \) is the set of non-active variables, \( 1 \) is a vector of ones, \( \eta \) is a positive constant vector, \( \text{sign}(\beta^{(1)}) \) stands for the sign of the coefficients of active variables, and the inequality holds element-wise.

A matrix which breaks this condition called non-irrepresentable (Zhao and Yu, 2006), and leads to inconsistent variable selection. In order to understand how serious of an issue this is in practice, we studied the non-irrepresentable condition across three types of real genomic data for three cancer types. All data comes from TCGA (http://cancergenome.nih.gov/). These datasets are moderately large: 617, 504 and 595 patients for the Glioblastoma, Lung and Breast datasets, respectively. The datasets also contain a high number of explanatory variables: 17,814 for gene expression, 27,577 for methylation and 4,201 for miRNA. As the data are drawn from multiple assay and cancer types, they can be considered a representative sample of genomic datasets one might encounter in practice.

We tested the non-irrepresentable condition on these datasets as follows: Using the real data as the design matrix \( X \), we selected \( K \) random genes to be ‘active’ in a simulated linear regression model. Then we checked the irrepeatability condition Equation (1) with \( \eta = 10^{-5} \) based on this active set. We replicated this 100 times for \( K = 1, 2, 5, 10, 50, 100 \) and Figure 1 illustrates the proportion of simulations that were non-irrepresentable and hence inconsistent for the Lasso. In all datasets, at least one active set broke this condition for each \( K \) and for \( K > 10 \), almost all active sets broke this condition.

To check the instability condition, we also calculated the frequency of highly correlated variables in the data. Six of the nine datasets checked had at least one pair of variables that had an empirical correlation coefficient of 0.99 or higher. These experiments indicate that both non-irrepresentability and high correlation—and hence inconsistency and instability—are both prevalent and a serious nuisance in working with real genomic datasets, motivating the need for more powerful methods that are robust to these problems.

2 Materials and methods

In this section, we introduce the Precision Lasso, a regularized regression method that mitigates the problems exposed in the previous section. We first introduce techniques to handle instability and inconsistency separately, and then combine these two approaches in order to derive the final model.
In this section, we validate the performance of our proposed Precision Lasso algorithm by comparing it to other variable selection methods. We compare the full Precision Lasso (PL) to a lightweight version that only uses the inverse covariance matrix in the regularizer (IC), which amounts to setting \( \gamma = 0 \). This version effectively considers only linear dependent variables, and helps to contrast the added benefits of considering both properties versus either alone. We also compare to the following baselines: Wald Hypothesis Testing, Sure Independence Screening (SIS) (Fan and Lv, 2008), Lasso regression, Ridge regression (RR), Elastic Net (EN), Adaptive Lasso (AL), SCAD, MCP and trace Lasso (TL). For the adaptive Lasso, we used the method introduced in Huang et al. (2008) to allow it to be applied to high-dimensional data. As the non-negative garrote does not work in the high dimension regime (Yuan and Lin, 2007), it was not included in our simulations.

To compare these methods, we ran the following experiments: (i) Simulated data with a continuous response, (ii) simulated case-control data using logistic regression and (3) breast cancer expression data. We report here the results for binary case-control data, although the results for continuous data are similar (details of all the experiments can be found in the Supplementary Material).

3.1 Simulation data

To simulate input data with high correlation between covariates, we use an auto-regressive sampling scheme (see Supplementary Sections S3.1 for details). We report here the average AUC score (area under ROC curve) for case-control data. Following the convention of Wu et al. (2009) to select the parameter \( \lambda \) (the weight of regularizer) by the number of selected variables, we select exactly \( K = k \) variables where \( k \) is the number of active variables in synthetic data. This helps to avoid overly complex models, which tend to selected by automatic measures such as cross-validation and AIC/BIC (Meinshausen and Bühlmann, 2006). Moreover, it is well-known that prediction performance and parameter estimation performance are not directly related. For example, the unstable and inconsistent problems that are the main focus of this paper illustrates this point: Good performance in prediction may be achieved by selecting correlated variables or linearly dependent variables, even though these variables may not be directly related to the response. For the Precision Lasso, the extra parameter \( \gamma \) is set as the prevalence of correlated variables divided by the prevalence of linearly dependent variables.

On data simulated from a binary logistic model, we see higher AUC for the Precision Lasso methods than for the baseline methods in the cases when auto-regressive coefficient is strong (Fig. 2). Interestingly, we can see that in the case where auto-regressive correlation is low (i.e. the setting for which the Precision Lasso was not originally intended), the Precision Lasso performs inferior to other methods. We further test for many other evaluation criterion including true positives, false positives, precision, recall and F1 score. The entire table can be found in the Supplementary Material (Supplementary Table S1). The Precision Lasso shows superior performance over the competing methods when the auto-regressive correlation is high.

We also tested the performance of these methods for continuous response data. Here, we observed that the Precision Lasso outperformed other methods, even more so relative to our experiments on case-control data (Supplementary Fig. S2). Similar to case-control data, the Precision Lasso behaves slightly worse than other competing methods when the correlation is low, but achieves clearly better
performance than competing methods when correlation is high. Additionally, one may notice that SIS behaves only slightly worse than Precision Lasso in Figure 2 on case-control data, but in Supplementary Figure S2, we observe a clear advantage of Precision Lasso over SIS. The gap between these two methods can be more clearly compared in Supplementary Table S2, where we present a detailed evaluation of all the methods along with other metrics.

We also tested Precision Lasso in several other settings, including mis-specified number of active variables (i.e. $K = k/2$ and $K = 2k$). We see that the Precision Lasso again outperforms the baseline methods in settings of large auto-correlation. Finally, we also compare the strategies for tuning hyperparameters to verify the argument that cross-validation is a less favourable parameter tuning strategy for variable selection. Detailed results are reported in Supplementary Section S6 of the Supplementary Material.

3.2 Breast cancer transcriptomic data

3.2.1 Data

To investigate the performance of Precision Lasso on real genomic data, we use breast cancer mRNA expression data from TCGA (http://cancergenome.nih.gov/) as explanatory variables and the case-control status as the phenotype. These data consist of RNA-seq assays for 532 breast cancer samples and 63 matching control samples. While it is typical to perform significant pre-processing on these data, here we are interested in the performance of statistical methods to extract signal from data with structured noise. For this reason, we perform variable selection on the FPKM-normalized RNA-seq counts of 10 000 genes.

3.2.2 Evaluation

For each variable selection method, we select exactly 100 genes. To evaluate the quality of these selections, we seek to identify genes that are likely to be involved in the causation of the breast cancer. First, we filter the selected genes by intersection with the Catalogue of Somatic Mutations in Cancer (Forbes et al., 2015) (COSMIC). Next, we use the results of a recent analysis (Rajendran and Deng, 2017) which combined annotations in COSMIC, IntOGen (Gonzalez-Perez et al., 2013), CBioPortal (Cerami et al., 2012) and OASIS (http://oasis-genomics.org/) to generate a list of potential driver mutations in breast cancer and cross-check each selected gene for evidence of driver function. The results are shown in Table 1.

3.2.3 Results

As seen in Table 1, the Precision Lasso effectively selected genes that have been linked to breast cancer. Not only did the Precision Lasso identify at least as many genes with known oncogenic somatic mutations as the baseline methods did, the associations selected by the Precision Lasso are also more likely to be causally related to breast cancer. For example, the Precision Lasso selected $\text{FOXA1}$ and $\text{AR}$, which both have been implicated as potential driver mutations in breast cancer and cross-check each selected gene for evidence of driver function. The results are shown in Table 1.

![Fig. 2. AUC of each variable selection method. Methods are: Wald Hypothesis Testing (Wald), Sure Independence Screening (SIS), Lasso, Ridge Regression (RR), Elastic Net (EN), Adaptive Lasso (AL), SCAD, MCP, Trace Lasso (TL), Inverse Covariance Regularizer (IC) and Precision Lasso (PL). The vertical axis represents area under ROC of the variable selection. The results are averaged from ten runs and SD is also shown. From the plot, we can see that our methods (PL and IC) exhibit a clear advantage over traditional methods on simulation data. Please notice that the AUC is calculated for variable selection task, instead of prediction of binary outcomes.](image-url)
dependent variables, as in the case of breast cancer RNA-seq assays. Furthermore, a gene-specific investigation suggests that while many genes are correlated with breast cancer oncogenesis, few have significant evidence of causality. In this setting, in which there are many variables that are linearly dependent or highly correlated, baseline methods tend to select variables which mediate the causal relationship between genotype and phenotype, as opposed to potential driver mutations that are of more interest to biologists. In contrast, the Precision Lasso tends to select these underlying driver mutations.

## 4 Discussion and Conclusion

While the Precision Lasso has been shown to outperform existing methods on variable selection tasks with highly correlated and linearly dependent data, it is also of interest to compare the relative computational efficiency of the compared methods. Owing to the complexity of the regularizer employed by the Precision Lasso, it is not surprising that it requires more computational resources, scaling cubically with the number of samples and linearly with the number of explanatory variables. Empirically, we find our implementation feasible of a dataset as large as $n = 1000$ with $p = 5000$ on a modern laptop (2.60 GHz CPU and 16 G RAM, Linux OS) or $n = 5000$ with $p = 50000$ on a modern server (2.30 GHz CPU and 128 G RAM, Linux OS). Furthermore, even though the Precision Lasso shows improvements in variable selection, it does not necessarily outperform traditional methods such as the Lasso in prediction. This is unsurprising, since the much simpler task of prediction does not suffer from the \textit{unstable} and \textit{inconsistent} problems that are unique to variable selection.

In this paper, we studied the problem of variable selection for genomic data in which a portion of the explanatory variables are either highly correlated or linearly dependent. In this setting, traditional variable selection methods such as the Lasso struggle with \textit{unstable} and \textit{inconsistent} selection. We first showed that these issues are quite real and arise in genomic datasets as a rule rather than an exception. To overcome these challenges, we proposed the Precision Lasso, a novel form of sparse regularization that overcomes many of the drawbacks of traditional methods such as the Lasso. In our experiments, the Precision Lasso outperformed these traditional methods in the presence of highly correlated and linearly dependent variables. With real breast cancer gene expression data, we demonstrated the effectiveness of the Precision Lasso to select more meaningful genes.

The Precision Lasso also offers the potential for extension to other structured methods. In particular, we are interested to see how this variable selection method can help improve structured variable selection methods such as the group lasso (Friedman et al., 2010) and graph fused lasso (Kim and Xing, 2009), as well as population stratification (Wang and Yang, 2016). We are also interested in improving the Precision Lasso when no linearly dependent variables or correlated variables exist. In addition, we are interested to see how Precision Lasso, can help improve predictive performance, akin to Haws et al. (2015). In addition, as Bayesian methods are

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### Table 1. Genes that were selected from breast cancer gene expression data and are annotated in the COSMIC dataset to have somatic mutations associated with tumours

| Method           | Selected gene | Tumor associations                  | Driver? |
|------------------|---------------|-------------------------------------|---------|
| Precision lasso  | FOXA1         | Breast, Prostate                    | ✓       |
|                  | AR            | Prostate                            | ✓       |
|                  | PBX1          | pre B-cell ALL, Myoepithelioma      |         |
|                  | COX4C         | Uterine leiomyoma                   |         |
| Wald test        | PPARG         | Follicular thyroid                  |         |
|                  | EBF1          | Lipoma                              |         |
|                  | TPM3          | Papillary thyroid; ALCL; NSCLC; Spitzoid tumour | |
| Lasso            | HMG2A         | Lipoma; Leiomysoma; Pleomorphic salivary gland adenoma | |
| Ridge regression | PPARG         | Follicular thyroid                  |         |
| Elastic net      | HMG2A         | Lipoma; Leiomysoma; Pleomorphic salivary gland adenoma | |
| adaptive lasso   | CBLC          | Acute Myeloid leukaemia             |         |
|                  | HMG2A         | Lipoma; Leiomysoma; Pleomorphic salivary gland adenoma | |
| SCAD             | GATA1         | Megakaryoblastic leukaemia of down syndrome | |
|                  | FCGR2B        | Acute lymphoblastic leukaemia       |         |
|                  | HMG2A         | Lipoma; Leiomysoma; Pleomorphic salivary gland adenoma | |
| MCP              | MYH1I         | Acute myeloid leukaemia             |         |
|                  | HMG2A         | Lipoma; Leiomysoma; Pleomorphic salivary gland adenoma | |
| Trace lasso      | FOXA1         | Breast, Prostate                    | ✓       |
|                  | EBF1          | Lipoma                              |         |
|                  | CDKN2A        | Melanoma                            |         |
|                  | COL1A1        | DFS, Aneurysmal bone cyst           |         |
| Inverse covariance | RAC1        | Carcinoma, Melanoma                 | ✓       |
|                  | TPR           | Papillary thyroid; NSCLC             |         |
|                  | ZNF384        | Acute lymphoblastic leukaemia       |         |

**Notes:** Genes with associations to breast cancer are bolded, and genes associated with high-confidence driver mutations are annotated in the rightmost column. Each method was constrained to select exactly 100 genes from a common set. We see that Precision Lasso selects the most relevant genes.
commonly believed to work best when the signal-to-noise ratio (SNR) is small—as is the case in genetic and genomic studies—a Bayesian extension of Precision Lasso is a promising direction for future research.

The Precision Lasso is open-source and freely available as a command line tool that is compatible with either .csv or PLINK files. We also plan to make the methodology available via a point-and-click interface by integrating it in the visual platform GenAMap (Wang et al., 2017).

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