Accounting for Linkage Disequilibrium in Genome-Wide Association Studies: A Penalized Regression Method

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Abstract

Penalized regression methods are becoming increasingly popular in genome-wide association studies (GWAS) for identifying genetic markers associated with disease. However, standard penalized methods such as the LASSO do not take into account the possible linkage disequilibrium between adjacent markers. We propose a novel penalized approach for GWAS using a dense set of single nucleotide polymorphisms (SNPs). The proposed method uses the minimax concave penalty (MCP) for marker selection and incorporates linkage disequilibrium (LD) information by penalizing the difference of the genetic effects at adjacent SNPs with high correlation. A coordinate descent algorithm is derived to implement the proposed method. This algorithm is efficient in dealing with a large number of SNPs. A multi-split method is used to calculate the p-values of the selected SNPs for assessing their significance. We refer to the proposed penalty function as the smoothed MCP and the proposed approach as the SMCP method. Performance of the proposed SMCP method and its comparison with a LASSO approach are evaluated through simulation studies, which demonstrate that the proposed method is more accurate in selecting associated SNPs. Its applicability to real data is illustrated using data from a study on rheumatoid arthritis.

Keywords: Genetic association, Feature selection, Linkage disequilibrium, Penalized regression, Single nucleotide polymorphism.

1 Introduction

With the rapid development of modern genotyping technology, genome-wide association studies (GWAS) have become an important tool for identifying genetic factors underlying complex traits. From a statistical standpoint, identifying SNPs associated with a trait can be formulated as a variable selection problem in sparse, high-dimensional models. The traditional multivariate regression methods are not directly applicable to GWAS because the number of SNPs in an association study is usually much larger than the sample size.

The LASSO (least absolute shrinkage and selection operator) provides a computationally feasible way for variable selection in high-dimensional settings Tibshirani [1996]. Recently, this approach has been applied to GWAS for selecting associated SNPs Wu et al. [2009]. It has been shown that the LASSO is selection consistent if and only if the predictors meet the irrepresentable condition Zhao and Yu [2006]. This condition is stringent and there is no known mechanism to verify it in GWAS. Zhang and Huang Zhang and Huang [2008] studied the sparsity and the bias of the LASSO in high-dimensional linear regression models. It is shown that under reasonable conditions, the LASSO selects a model of the correct order of dimensionality. However, the LASSO tends to overselect unimportant variables. Therefore, direct application of the LASSO to GWAS tends to generate findings with high false positive rates. Another limitation of the LASSO is that, if there is a group of variables among which the pairwise correlations are high, then the LASSO tends to select only one variable from the group and does not care which one is selected Zou and Hastie [2005].

Several methods that attempt to improve the performance of the LASSO have been proposed. The adaptive LASSO Zou [2006] uses adaptive weights on each penalty so that the oracle properties hold under some mild regularity conditions. In the case that the number of predictors is much larger than sample size, adaptive weights cannot be initiated easily. Elastic net method Zou and Hastie [2005] can effectively deal with certain correlation structures in the predictors by using a combination of ridge and LASSO penalties. Fan and Li Fan and Li [2001] introduced a smoothly clipped absolute deviation (SCAD) method. Zhang Zhang [2010] proposed a flexible minmax concave penalty (MCP) which attenuates the effect of shrinkage that leads to bias. Both the SCAD and MCP belong to the same family of quadratic spline penalties and both lead to oracle selection results Zhang [2010].

The MCP has a simpler form and requires weaker conditions for the oracle property. We refer to Zhang [2010] and Mazumder et al. [2011] for detailed discussion.

However, the existing penalized methods for variable selection do not take into account the specifics of SNP data. SNPs are naturally ordered along the genome with respect to their physical positions. In the presence of linkage disequilibrium (LD), adjacent SNPs are expected to show similar strength of association. Making use of LD information from adjacent SNPs is highly desirable as it should help to better delineate association signals while reducing randomness seen in single SNP analysis. Fused LASSO Tibshirani et al. [2005] is not appropriate for this purpose, since the effect of association for a SNP (as measured by its regression coefficient) is only identifiable up to its absolute value – a homozygous genotype can be equivalently coded as either 0 or 2 depending on the choice of the reference allele.

We propose a new penalized regression method for identifying associated SNPs in GWAS. The proposed method uses a novel penalty, which we shall refer to as the smoothed minimax concave penalty, or SMCP, for sparsity and smoothness in absolute values. The SMCP is a combination of the MCP and a penalty consisting of the squared differences of the absolute effects of adjacent markers. The MCP promotes sparsity in the model and does automatic selection of associated SNPs. The penalty for squared differences of the absolute effects takes into account the natural ordering of SNPs and adaptively incorporates possible LD information between adjacent SNPs. It explicitly uses correlation between adjacent markers and penalizes the differences of the genetic effects at adjacent SNPs with high correlation. We derive a coordinate descent algorithm for implementing the SMCP method. We use a resampling method for computing p-values of the selected SNPs in order to assess their significance.

The rest of the paper is organized as follows. Section 2 introduces the proposed SMCP method. Section 3 presents a genome-wide screening incorporating the proposed SMCP method. Section 4 describes a coordinate descent algorithm for estimating model parameters and discusses selection of the values of the tuning parameters and p-value calculation. Section 5 evaluates the proposed method and a LASSO method using simulated data. Section 6 applies the proposed method to a GWAS on rheumatoid arthritis. Finally, Section 7 provides a summary and discusses some related issues.

2 The SMCP method

Let p be the number of SNPs included in the study, and let β_j denote the effect of the jth SNP in a working model that describes the relationship between phenotype and markers. Here we assume that the SNPs are ordered according to their physical locations on the chromosomes. Adjacent SNPs in high LD are expected to have similar strength of association with the phenotype. To adaptively incorporating LD information, we propose the following penalty that encourages smoothness in $|\beta|$s at neighboring SNPs:

$$\frac{\lambda_2}{2}\sum_{j=1}^{p-1}\zeta_j(|\beta_j| - |\beta_{j+1}|)^2, \tag{1}$$

where the weight ζ_j is a measure of LD between SNP j and SNP $(j+1)$. This penalty encourages $|\beta_j|$ and $|\beta_{j+1}|$ to be similar to an extent inversely proportional to the LD strength between the two corresponding SNPs. Adjacent SNPs in weak LD are allowed to have larger difference in their $|\beta|$s than if they are in stronger LD. The effect of this penalty is to encourage smoothness in $|\beta|$s for SNPs in strong LD. By using this penalty, we expect a better delineation of the association pattern in LD blocks that harbor disease variants while reducing randomness in $|\beta|$s in LD blocks that do not. We note that there is no monotone relationship between ζ and the physical distance between two SNPs. While it is possible to use other LD measures, we choose ζ_j to be the absolute value of lag one autocorrelation coefficient between the genotype scores of SNP j and SNP $(j+1)$. The values of ζ_j for rheumatoid arthritis data used by Genetic Analysis Workshop 16, the data set to be used in our simulation study and empirical study, are plotted for chromosome 6 (Fig. 1(a)). The proportion that $\zeta_j > 0.5$ over non-overlapping 100-SNP windows is also plotted (Fig. 1(b)).

[Figure 1 about here.]

For the purpose of SNP selection, we use the MCP, which is defined as

$$\rho(t; \lambda_1, \gamma) = \lambda_1 \int_0^{|t|} (1 - x/(\gamma\lambda_1))_+ dx,$$

where λ_1 is a penalty parameter and γ is a regularization parameter that controls the concavity of ρ. Here x_+ is the nonnegative part of x, i.e., $x_+ = x1_{\{x \geq 0\}}$. The MCP can be easily understood by considering its derivative, which is

$$\dot{\rho}(t; \lambda_1, \gamma) = \lambda_1 \big(1 - |t|/(\gamma\lambda_1)\big)_+ \mathrm{sgn}(t),$$

where $\mathrm{sgn}(t) = -1, 0,$ or 1 if $t < 0, = 0,$ or > 0, respectively. As $|t|$ increases from 0, MCP begins by applying the same rate of penalization as the LASSO, but continuously relaxes that penalization until $|t| > \gamma\lambda_1$, a condition under which the rate of penalization drops to 0. It provides a continuum of penalties where the LASSO penalty corresponds to $\gamma = \infty$ and the hard-thresholding penalty corresponds to $\gamma \to 1+$. We note that other penalties, such as the LASSO penalty or SCAD penalty, can also be used to replace MCP. We choose MCP because it possesses all the basic desired properties of a penalty function and is computationally simple Mazumder et al. [2011], Zhang [2010].

Given the parameter vector $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_p)'$ and a loss function $g(\boldsymbol{\beta})$ based on a working model for the relationship between the phenotype and markers, the SMCP in a working model can be expressed as minimizing the criterion

$$L_n(\boldsymbol{\beta}) = g(\boldsymbol{\beta}) + \sum_{j=1}^{p} \rho(|\beta_j|; \lambda_1, \gamma) + \frac{\lambda_2}{2} \sum_{j=1}^{p-1} \zeta_j (|\beta_j| - |\beta_{j+1}|)^2. \tag{2}$$

We minimize this objective function with respect to $\boldsymbol{\beta}$, while using a bisection method to determine the regularization parameters (λ_1, λ_2). SNPs corresponding to $\hat{\beta}_j \neq 0$ are selected as being potentially associated with disease. These selected SNPs will be subject to further analysis using a multi-split sampling method to determine their statistical significance, as described later.

3 Genome-wide screening incorporating LD

A basic method for GWAS is to conduct genome-wide screening of a large number of dense SNPs individually and look for those with significant association with phenotype. Although several important considerations, such as adjustment for multiple comparisons and possible population stratification, need to be taken into account in the analysis, the essence of the existing genome-wide screening approach is single-marker based analysis without considering the structure of SNP data. In particular, the possible LD between two adjacent SNPs are not incorporated in the analysis.

Our proposed SMCP method can be used for screening a dense set of SNPs incorporating LD information in a natural way. To be specific, here we consider the standard case-control design for identifying SNPs that potentially associated with disease. Let the phenotype be scored as 1 for cases and -1 for controls. Let n_j be the number of subjects whose genotypes are non-missing at SNP j. The standardized phenotype of the ith subject with non-missing genotype at SNP j is denoted by y_{ij}. The genotype at SNP j is scored as 0, 1, or 2 depending on the number of copies of a reference allele in a subject. Let x_{ij} denote the standardized genotype score satisfying $\sum_i x_{ij} = 0$ and $\sum_{i=1}^{n_j} x_{ij}^2 = n_j$.

Consider the penalized criterion

$$L_n(\boldsymbol{\beta}) = \frac{1}{2}\sum_{j=1}^{p}\frac{1}{n_j}\sum_{i=1}^{n_j}(y_{ij} - x_{ij}\beta_j)^2 + \sum_{j=1}^{p}\rho(|\beta_j|; \lambda_1, \gamma)$$

$$+\frac{\lambda_2}{2}\sum_{j=1}^{p-1}\zeta_j(|\beta_j|-|\beta_{j+1}|)^2. \tag{3}$$

Here the loss function is

$$g(\boldsymbol{\beta})=\frac{1}{2}\sum_{j=1}^{p}\frac{1}{n_j}\sum_{i=1}^{n_j}(y_{ij}-x_{ij}\beta_j)^2. \tag{4}$$

We note that switching the reference allele used for scoring the genotypes changes the sign of β_j but $|\beta_j|$ remains the same. It may be counter-intuitive to use a quadratic loss in (4) for case-control designs. We now show that this is appropriate. Regardless how the phenotype is scored, the least squares regression slope of the phenotype over the genotype score at SNP j (i.e., a regular single SNP analysis) equals

$$\sum_{i=1}^{n_j} y_{ij}x_{ij}/\sum_{i=1}^{n_j} x_{ij}^2 = 2(\hat{p}_{1j}-\hat{p}_{2j})/\phi_j(1-\phi_j),$$

where ϕ_j is the proportion of cases out of total subjects computed from the subjects with non-missing genotype and $\hat{p}_{1j}$ and $\hat{p}_{2j}$ are allele frequencies of the SNP j in cases and controls, respectively. This shows that the β_j in the squared loss function (4) can be interpreted as the effect size of SNP j. In the classification literature, quadratic loss has also been used for indicator response variables Hastie et al. [2009].

An alternative loss function for binary phenotype would be the sum of negative marginal log-likelihood based on a working logistic regression model. We have found that the selection results using this loss function are in general similar to those based on (4). In addition, the computational implementation of the coordinate descent algorithm described in the next subsection using the loss function (4) is much more stable and efficient and can easily handle tens of thousands SNPs.

4 Computation

In this section, we first present a coordinate descent algorithm for the proposed SMCP method. Then we discuss methods of selecting tuning parameters and evaluating p-values for the selected SNPs.

4.1 Coordinate Descent Algorithm

In this part, we derive a coordinate descent algorithm for computing the solution to (3). This algorithm was originally proposed for criterions with convex penalties such as LASSO Knight and Fu [2000], Friedman et al. [2010], Wu and Lange [2007]. It has been proposed to calculate nonconvex penalized regression estimates Mazumder et al. [2011], Breheny and Huang [2011]. This algorithm optimizes a target function with respect to one parameter at a time, iteratively cycling through all parameters until convergence is reached. It is particularly suitable for problems such as the current one that have a simple closed form solution in a single dimension but lack one in higher dimensions.

We wish to minimize the objective function $L_n(\boldsymbol{\beta})$ in (3) with respect to β_j while keeping all other $\beta_k, k \neq j$, fixed at their current estimates. Thus only the terms involving β_j in L_n matter. That is, this problem is equivalent to minimizing $R(\beta_j)$ defined as

$$\begin{aligned} R(\beta_j) &= \frac{1}{2n_j}\sum_{i=1}^{n_j}(y_{ij} - x_{ij}\beta_j)^2 + \rho(|\beta_j|; \lambda_1, \gamma) \\ &\quad + \frac{1}{2}\lambda_2[\zeta_j(|\beta_j| - |\tilde{\beta}_{j+1}|)^2 + \zeta_{j-1}(|\tilde{\beta}_{j-1}| - |\beta_j|)^2] \\ &= C + a_j\beta_j^2 + b_j\beta_j + c_j|\beta_j|, \quad j = 2, \dots, p-1, \end{aligned}$$

where C is a term free of β_j, $\tilde{\beta}_{j+1}$ and $\tilde{\beta}_{j-1}$ are current estimates of β_{j+1} and β_{j-1}, respectively, and a_j, b_j, and c_j are determined as follows:

- For $|\beta_j| < \gamma\lambda_1$,

$$a_j = \frac{1}{2}\left(\frac{1}{n_j}\sum_{i=1}^{n_j} x_{ij}^2 + \lambda_2(\zeta_{j-1}+\zeta_j) - \frac{1}{\gamma}\right),$$
$$b_j = -\frac{1}{n_j}\sum_{i=1}^{n_j} x_{ij}y_{ij},$$

  and

$$c_j = \lambda_1 - \lambda_2(|\tilde{\beta}_{j+1}|\zeta_j + |\tilde{\beta}_{j-1}|\zeta_{j-1}). \tag{5}$$

- For $|\beta_j| \geq \gamma\lambda_1$,

$$a_j = \frac{1}{2}\left(\frac{1}{n_j}\sum_{i=1}^{n_j} x_{ij}^2 + \lambda_2(\zeta_{j-1}+\zeta_j)\right),$$
$$c_j = -\lambda_2(|\tilde{\beta}_{j+1}|\zeta_j + |\tilde{\beta}_{j-1}|\zeta_{j-1}), \tag{6}$$

  while b_j remains the same as in the previous situation.

Note that function $R(\beta_j)$ is defined for $j \neq 1, p$. It can be defined for $j = 1$ by setting $\tilde{\beta}_{j-1} = 0$ and for $j = p$ by setting $\tilde{\beta}_{j+1} = 0$ in the above two situations.

Minimizing $R(\beta_j)$ with respect to β_j is equivalent to minimizing $a_j\beta_j^2 + b_j\beta_j + c_j|\beta_j|$, or equivalently,

$$a_j\left(\beta_j + \frac{b_j}{2a_j}\right)^2 + c_j|\beta_j|. \tag{7}$$

The first term is convex in β_j if $a_j > 0$. In the case $|\beta_j| \geq \gamma\lambda_1$, $a_j > 0$ is trivially true. In the case $|\beta_j| < \gamma\lambda_1$, $a_j > 0$ holds when $\gamma > 1$.

Let $\hat{\beta}_j$ denote the minimizer of $R(\beta_j)$. It has the following explicit expression:

$$\hat{\beta}_j = -\mathrm{sign}(b_j)\cdot\frac{(|b_j| - c_j)_+}{2a_j}. \tag{8}$$

This is because if $c_j > 0$, minimizing (7) becomes a regular one dimensional LASSO problem. $\hat{\beta}_j$ is the soft-threshold operator. If $c_j < 0$, it can be shown that $\hat{\beta}_j$ and b_j are of opposite sign. If $b_j \geq 0$, expression (7) becomes

$$a_j \left(\beta_j + \frac{b_j}{2a_j} \right)^2 - c_j \beta_j.$$

Hence $\hat{\beta}_j = -(b_j - c_j)/2a_j < 0$. If $b_j < 0$, then $|\hat{\beta}_j| = \hat{\beta}_j$ and $\hat{\beta}_j = -(b_j + c_j)/2a_j > 0$. In summary, expression (8) holds in all situations.

The novel penalty (1) affects both a_j and c_j. Both $2a_j$ and c_j are linear in λ_2. As λ_2 increases, $2a_j$ increases at rate $\partial(2a_j)/\partial\lambda_2 = \zeta_{j-1} + \zeta_j$ while c_j decreases at rate $\partial c_j/\partial\lambda_2 = |\tilde{\beta}_{j+1}|\zeta_j + |\tilde{\beta}_{j-1}|\zeta_{j-1}$. In the case of $|b_j| - c_j \geq 0$, these are the rates of change for the denominator and the numerator of $|\hat{\beta}_j| = (|b_j| - c_j)_+/(2a_j)$. The change in $|\hat{\beta}_j|$ more complicated as it involves the intercepts of its numerator and denominator. In terms of $|\tilde{\beta}_{j+1}|$ and $|\tilde{\beta}_{j-1}|$, $\hat{\beta}_j$ is larger when these two values are larger. Since b_j does not depend on λ_2, more SNPs will satisfy $|b_j| - c_j \geq 0$ and thus be selected as λ_2 increases.

We note that a_j and b_j do not depend on any β_j. They only need to be computed once for each SNP. Only c_j needs to be updated after all β_js are updated. In the special case of $\lambda_2 = 0$, the SMCP method becomes the MCP method. Even c_j no longer depends on $\tilde{\beta}_{j-1}$ and $\tilde{\beta}_{j+1}$: $c_j = \lambda_1$ if $|\beta_j| < \gamma\lambda_1$ and $c_j = 0$ otherwise. Expression (8) gives the explicit solution for β_j.

Generally, an iterative algorithm is required to estimate these parameters. Let $\tilde{\boldsymbol{\beta}}^{(0)} = (\tilde{\beta}_1^{(0)}, \ldots, \tilde{\beta}_p^{(0)})'$ be the initial value of the estimate of $\boldsymbol{\beta}$. The proposed coordinate descent algorithm proceeds as follows:

1. Compute a_j and b_j for $j = 1, \ldots, p$.

2. Set $s = 0$.

3. For $j = 1, \ldots, p$,

    (a) Compute c_j according to expressions (5) or (6).

(b) Update $\tilde{\beta}_j^{(s+1)}$ according to expression (8).

4. Update $s \leftarrow s+1$.

5. Repeat steps (3) and (4) until the estimate of $\boldsymbol{\beta}$ converges.

In practice, the initial values $\beta_j^{(0)}, j = 1, \ldots, p$ are set to 0. Each β_j is then updated in turn using the coordinate descent algorithm described above. One iteration completes when all β_js are updated. In our experience, convergence is typically reached after about 30 iterations for the SMCP method.

The convergence of this algorithm follows from Theorem 4.1(c) of Tseng [2001]. This can be shown as follows. The objective function of SGL can be written as $f(\boldsymbol{\beta}) = f_0(\boldsymbol{\beta}) + \sum_{j=1}^{J} f_j(\beta_j)$ where

$$f_0(\boldsymbol{\beta}) = \frac{1}{2}\sum_{j=1}^{p}\frac{1}{n_j}\sum_{i=1}^{n_j}(y_{ij} - x_{ij}\beta_j)^2 + \frac{\lambda_2}{2}\sum_{j=1}^{p-1}\zeta_j(|\beta_j| - |\beta_{j+1}|)^2,$$

and $f_j(\beta_j) = \rho(|\beta_j|; \lambda_1, \gamma)$. Since f is regular in the sense of (5) in Tseng (2001) and $\sum_{j=1}^{J} f_j(\beta_j)$ is separable , the GCD solutions converge to a coordinatewise minimum point of f, which is also a stationary point of f.

For now, the property of the second penalty is discussed. We assume that currently, λ_1 and λ_2 are fixed and we want to solve the objective function (2). Suppose that in the most recent step $(s-1)$, β_{j-1} was updated and compare the value of estimates under adjacent steps, $\delta = |\tilde{\beta}_{j-1}^{(s)}| - |\tilde{\beta}_{j-1}^{(s-1)}|$.We further assume that at the most recent step $(s-1)$, only $\tilde{\beta}_{j-1}^{(s-1)}$ is non-zero and δ is usually positive. We now go into the step s to update β_j.

- If $\mathrm{corr}(x_j, x_{j-1}) > 0$, then $\zeta_{j-1} = \mathrm{corr}(x_j, x_{j-1})$. We have $c_j^{(s)} = c_j^{(s-1)} - \lambda_2\delta\zeta_{j-1}$. Note that $c_j^{(s)} < c_j^{(s-1)}$, since $\zeta_{j-1} > 0$. From expressions(8), we know that $\beta_j^{(s)}$ will be non-zero if c_j is less than $|b_j|$. One can see that with stronger correlation (i.e. ζ_{j-1} is larger) and/or λ_2 is larger, $c_j^{(s)}$ is smaller. Consequently, $\tilde{\beta}_j^{(s)}$ is more likely to be non-zero. The sign of $\tilde{\beta}_j$ is also positive if it is not zero. It makes sense that the correlation between $(j-1)$th and jth predictors is assumed to be positive.

- It is similar when $\text{corr}(x_j, x_{j-1}) < 0$.

Thus, incorporating the second penalty increases the chance that adjacent SNPs with high correlation to be selected together.

4.2 Tuning parameter selection

Selecting appropriate values for tuning parameters is important. It affects not only the number of selected variables but also the estimates of model parameters and the selection consistency. There are various methods that can be applied, which include AIC Akaike [1974], BIC Schwarz [1978], Chen and Chen [2008], cross-validation and generalized cross-validation. However, they are all based upon the the performance of prediction error. In GWAS, disease markers may not be in the set of SNP markers. Practically it is rare that disease markers are part of SNPs data, which consequently results in non-true model for SNPs data. Hence, the methods mentioned above may be inadequate in GWAS. Wu et al. Wu et al. [2009] used a predetermined number of predictors to select the tuning parameter and implement a combination of bracketing and bisection to search for the optimal tuning parameter. We adopt Wu et al. [2009] method to select tuning parameters. For this purpose, tuning parameters λ_1 and λ_2 are re-parameterized through $\tau=\lambda_1+\lambda_2$ and $\eta=\lambda_1/\tau$. The value of η is fixed beforehand. When $\eta = 1$, the SMCP method becomes the MCP method.

The optimal value of τ that selects the predetermined number of predictors is determined through bisection as follows. Let $r(\tau)$ denote the number of predictors selected under τ. Let $\tau_{\max}$ be the smallest value for which all coefficients are 0. $\tau_{\max}$ is the upper bound for τ. From

(5), $\tau_{\max} = \max_j |\sum_{i=1}^{n_j} x_{ij} y_{ij}|/(n_j \eta)$. To avoid undefined saturated linear models, τ can not be 0 or close to 0. Its lower bound, denoted by $\tau_{\min}$, is set at $\tau_{\min} = \epsilon \tau_{\max}$ for preselected ϵ. Setting $\epsilon = 0.1$ seems to work well with the SMCP method. Initially, we set $\tau_l = \tau_{min}$ and $\tau_u = \tau_{max}$. If $r(\tau_u) < s < r(\tau_l)$, then we employ bisection. This involves testing the midpoint $\tau_m = \frac{1}{2}(\tau_l + \tau_u)$. If $r(\tau_m) < s$, we replace τ_u by τ_m. If $r(\tau_m) > s$, we replace τ_l by τ_m. This process repeats until $r(\tau_m) = s$. From simulation study, we find that regularization parameter γ also has an important impact on the analysis. Based on our experience, $\gamma = 6$ is a reasonable choice for the SMCP method.

4.3 *P*-values for the selected SNPs

The use of p-value is a traditional way to evaluate the significance of estimates. However, there are no straightforward ways to compute standard error of penalized linear regression estimates. Wu et al. Wu et al. [2009] proposed a leave-one-out approach for computing p-values by assessing the correlations among the selected SNPs in the reduced model. We use the multi-split method proposed by Meinshausen et al. [2009] to obtain reproducible p-values. This is a simulation-based method that automatically adjusts for multiple comparisons.

In each iteration, the multi-split method proceeds as follows:

1. Randomly split the data into two disjoint sets of equal size: D_{in} and D_{out}. The case:control ratio in each set is the same as in the original data.

2. Fit the SMCP method with data in D_{in}. Denote the set of selected SNPs by S.

3. Assign a p-value $\tilde{P}_j$ to SNP j in the following way:

   (a) If SNP j is in set S, set $\tilde{P}_j$ to be its p-value on D_{out} in the regular linear regression where SNP j is the only predictor.

(b) If SNP j is not in set S, set $\tilde{P}_j = 1$.

4. Define adjusted p-value by $P_j = \min\{\tilde{P}_j|S|, 1\}, j = 1, \ldots, p$, where $|S|$ is the size of set S.

This procedure is repeated B times for each SNP. Let $P_j^{(b)}$ denote the adjusted p-value for SNP j in the bth iteration. For $\pi \in (0, 1)$, let q_π be the π-quantile on $\{P_j^{(b)}/\pi; b = 1, \ldots, B\}$. Define $\tilde{Q}_j(\pi) = \min\{1, q_\pi\}$. Meinshausen et al. [2009] proved that $\tilde{Q}_j(\pi)$ is an asymptotically correct p-value, adjusted for multiplicity. They also proposed an adaptive version that selects a suitable value of quantile based on the data:

$$Q_j = \min\{1, (1 - \log \pi_0) \inf_{\pi \in (\pi_0, 1)} \tilde{Q}_j(\pi)\},$$

where π_0 is chosen to be 0.05. It was shown that $Q_j, j = 1, \ldots, p$, can be used for both FWER (family-wise error rate) and FDR control Meinshausen et al. [2009].

5 Simulation studies

To make the LD structure as realistic as possible, genotypes are obtained from a rheumatoid arthritis (RA) study provided by the Genetic Analysis Workshop (GAW) 16. This study involves 2062 individuals. Four hundred of them are randomly chosen. Five thousand SNPs are selected from chromosome 6. For individual i, its phenotype y_i is generated as follows:

$$y_i = \boldsymbol{x}_i'\boldsymbol{\beta} + \epsilon_i, \quad i = 1, \ldots, 400,$$

where x_i (a vector of length 5000) represents the genotype data of individual i, $\boldsymbol{\beta}$ is the vector of genetic effect whose elements are all 0 except that $(\beta_{2287}, \ldots, \beta_{2298}) = (0.1, 0.2, -0.1, 0.2, 1, -0.1, -1, 0.1, -1, 0.1, -0.6, 0.2)$ and $(\beta_{2300}, \ldots, \beta_{2318}) = (0.1, -0.6, 0.2, 0.3, -0.1, 0.3, 0.4, -1.2, 0.1, 0.3, -0.7, 0.1, 1, 0.2, -0.4, 0.1, 0.5, -0.2, 0.1)$. ϵ_i is the residual sampled from a normal distribution with mean 0 and standard deviation 1.5. The loss function $g(\boldsymbol{\beta})$ is given in expression (4).

To evaluate the performance of SMCP, we use false discovery rate (FDR) and false negative rate (FNR) which are defined as follows. Let $\hat{\beta}_j$ denote the estimated value of β_j,

$$\text{FDR} = \frac{\#\text{ of SNPs with } \hat{\beta}_j \neq 0 \text{ but } \beta_j = 0}{\#\text{ of SNPs with } \hat{\beta} \neq 0}$$

and

$$\text{FNR} = \frac{\#\text{ of SNPs with } \hat{\beta}_j = 0 \text{ but } \beta_j \neq 0}{\#\text{ of SNPs with } \beta \neq 0}.$$

[Table 1 about here.]

The mean and the standard deviation of the number of true positives, FDR and FNR for various values of η for the SMCP method and a LASSO method over 100 replications are reported in Table 1. In each replication, 50 SNPs are selected. It can be seen that for different value of η, FDR and FNR change in the same direction, since the number of the selected SNPs is fixed. As the number of true positives increases, the number of false negatives and the number of false positives decrease. Overall, the SMCP method outperforms the LASSO in terms of true positives and FDR.

[Table 2 about here.]

To investigate further the performance of the SMCP method and the LASSO method, we look into a particular simulated data set. The 50 SNPs selected by the SMCP method and their p-values obtained using the multi-split method are reported in Table 2. It is apparent that the number of true positives is much higher for the SMCP method than for the LASSO method. SMCP selects 25 out of 31 true disease associated SNPs while LASSO selects 21. Note that multi-split method can effectively assign p-values for the selected SNPs: All the non-disease associated SNPs are insignificant for the SMCP method. In conparison, two SNPs (SNP 2320 and SNP 2321) are significant for the LASSO method.

6 Application to Rheumatoid Arthritis Data

Rheumatoid arthritis (RA) is a complex human disorder with a prevalence ranging from around 0.8% in Caucasians to 10% in some native American groups Amos et al. [2009]. Its risk is generally higher in females than in males. Some studies have identified smoking as a risk factor. Genetic factors underlying RA have been mapped to the HLA region on region 6p21 Newton et al. [2004], PTPN22 locus at 1p13 Begovich et al. [2004], and the CTLA4 locus at 2q33 Plenge et al. [2005]. There are some other loci reported. These loci are at 6q (TNFAIP3), 9p13 (CCL21), 10p15 (PRKCQ), and 20q13 (CD40) and seem to be of weaker effects Amos et al. [2009].

GAW 16 RA data is from the North American Rheumatoid Arthritis Consortium (NARAC). It is the initial batch of whole genome association data for the NARAC cases (N=868) and controls (N=1194) after removing duplicated and contaminated samples. The total sample size is 2062. After quality control and removing SNPs with low minor allele frequency, there are 475672 SNPs over 22 autosomes, of which 31670 are on chromosome 6.

The SNPs on the whole genome are analyzed simultaneously. By using different numbers for predetermined number of SNPs, we found that 800 SNPs along the genome are appropriate for the GAW 16 RA dataset. For the SMCP method, the optimal value for tuning parameter τ corresponding to this setting is 1.861 with $\eta = 0.05$. p-values of the selected SNPs are computed using multi-split method. The majority of the SNPs (539 out of 800) selected by the SMCP method are on chromosome 6, 293 of which are significant at significance level 0.05. The plot of $-\log_{10}(p\text{-value})$ for the selected SNPs against their physical positions is shown in Fig. 2(a) for chromosome 6.

For the LASSO method (i.e., $\eta = 1$ and $\gamma = \infty$), the same procedure is implemented to select 800 SNPs across the genome. The optimal value for tuning parameter τ is 0.091.

There are 537 SNPs selected on chromosome 6 and 280 of them are significant with multi-split p-value less than 0.05. The plot of $-\log_{10}(p\text{-value})$ for chromosome 6 is shown in Fig. 2(b).

We also analyzed the data using the MCP method (i.e., $\eta = 1$). It selects the same set of SNPs as the LASSO method. The difference of the LASSO and the MCP lies in the magnitude of estimates, since the MCP is unbiased under proper choice of γ but the LASSO is always biased. Two sets of SNPs selected by the SMCP and the LASSO, respectively, on chromosome 6 are both in the region of HLA-DRB1 gene that has been found to be associated with RA Newton et al. [2004].

There are SNPs on other chromosomes that are significant or close to be significant (Table 3). Particularly, association to rheumatoid arthritis at SNP rs2476601 in gene PTPN22 has been reported previously Begovich et al. [2004]. Other noteworthy SNPs include SNP rs512244 in RAB28 region, 4 SNPs in TRAF1 region, SNP rs12926841 in CA5A region, SNP rs3213728 in RNF126P1 region, and SNP rs1182531 in PHACTR3 region. On chromosome 9, 4 SNPs in the region of TRAF1 gene are identified by the SMCP method and the LASSO method. The estimates of βs obtained from SMCP, MCP, LASSO and the regular single-SNP linear regression analysis are presented in Fig. 3. One can see from Fig. 3, the MCP method produce larger estimates than the LASSO method, but the estimates from the SMCP method are smaller than those from the LASSO. This is caused by the (side) shrinkage effect of the proposed smoothing penalty. In terms of model selection, SMCP tends to select more adjacent SNPs that are in high LD.

[Figure 2 about here.]

[Figure 3 about here.]

[Table 3 about here.]

7 Discussion

Penalized method is a modern variable selection approach developed to handle "large p, small n" problems. Application of this approach to GWAS is highly anticipated. Compared to traditional GWAS where each SNP is analyzed one at a time, penalized method is able to handle a collection of SNPs at the same time. We have proposed a novel SMCP penalty and introduced a penalized regression method suited to GWAS. A salient feature of this method is that it takes into account the LD among SNPs in order to reduce the randomness often seen in the traditional one-SNP-at-a-time analysis. We developed a coordinate descent algorithm to implement the proposed SMCP method. Also, we applied a multi-split method to compute p-values which can be used to assess the significance of selected SNPs.

The proposed SMCP method is different from the fused LASSO. The objective function for fused LASSO can be written

$$g(\boldsymbol{\beta}) + \lambda_1 \sum_{j=1}^{p} |\beta_j| + \lambda_2 \sum_{j=1}^{p-1} |\beta_{j+1} - \beta_j|.$$

One apparent difference between SMCP and fused LASSO is in the second penalty. SMCP uses a L_2 penalty on the absolute difference which makes soft smoothing. In comparison fused LASSO uses L_1 for the smoothing penalty. Hence, it will put adjacent parameters to be exactly the same. Second, SMCP is not affected by the choice of reference allele for genotype scoring. Third, SMCP explicitly incorporate a measure of LD of adjacent SNPs to only encourage smoothness of the effects of those with high LD. This feature of the penalty is particularly suitable for GWAS. Fourth, SMCP is computationally efficient as it has an explicit solution when updating β_j. In comparison, no such explicit solution exists for fused LASSO. Its computation is not as efficient as SMCP even using the method proposed by Friedman et al. [2007].

A thorny issue in handling large number of SNPs simultaneously is computation. We used several measures to tackle this issue. We introduced explicit expressions for implementing the coordinate descent algorithm. This algorithm is stable and efficient in our simulation studies and data example. For a dichotomous phenotype, we showed that a marginal quadratic loss function yields correct estimate of the effect of a SNP. Two important advantages in using the marginal loss (4) instead of a joint loss are its convenience in computing over genome and handling missing genotypes, a phenomenon common in high-throughput genotype data. As the expression (5) indicates, only c_j needs to be updated for each iteration. Thus, there is no need to read all the data on 22 chromosomes in a computer. The inner products between standardized phenotypes and genotypes are all needed. It makes computing for all SNPs over genome possible. Second, joint loss function does not allow any missing genotypes. Missing genotypes have to be imputed upfront, incurring extra computation time and uncertainty in imputed genotypes. In contrast, the marginal loss function (4) is not impeded by missing genotypes.

Compared with the LASSO, the proposed SMCP method is able to incorporate the consecutive absolute difference to the penalty. Simulation studies show that the SMCP method is superior to LASSO in the context of GWAS in terms of model size and false negative rate.

We have focused on the case of a dichotomous phenotype in GWAS. The basic idea of our method can be applied to the analysis of quantitative traits, based on a linear regression model and a least squares loss function. Furthermore, covariates and environmental factors, including those derived from principal components analysis based on marker data for adjusting population stratification, can be incorporated in the SMCP analysis. Specifically, we can consider a loss function that includes the effects of the SNPs and the covariate effects based on an appropriate working regression model, then use the SMCP penalty on the coefficients of the SNPs. The coordinate descent algorithm for the SMCP method and the multi-split method for assessing statistical significance can be used in such settings with some modifications.

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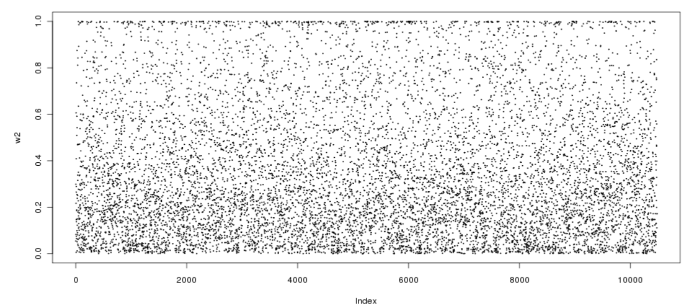
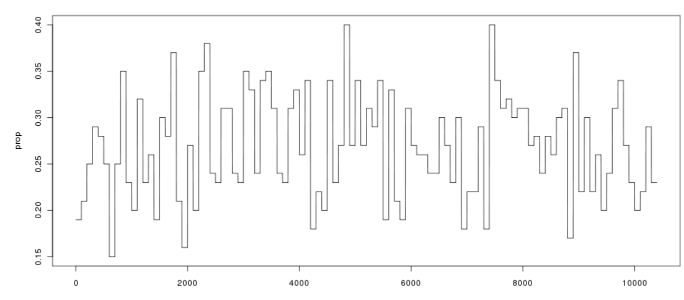
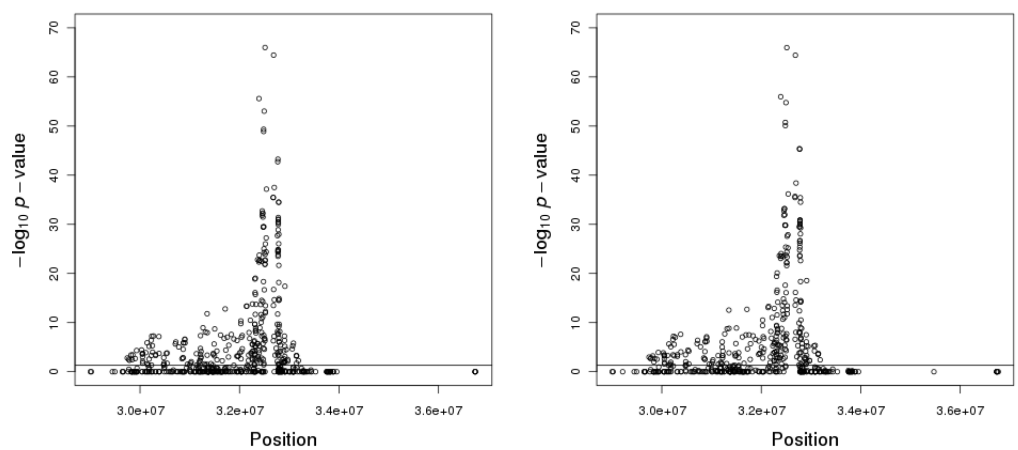


(a) Absolute lag-one autocorrelation ζ_j



(b) Absolute lag-one autocorrelation coefficients larger than 0.5 averaged within non-overlapping 100-SNPs windows.

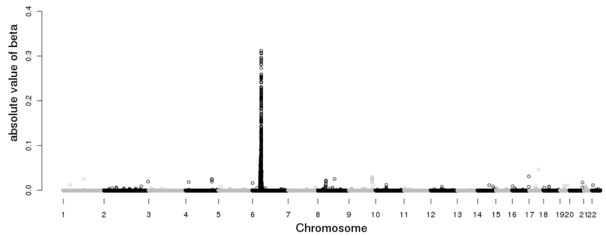
Figure 1: Plots of absolute lag-one autocorrelation ζ_j on Chromosome 6 from Genetic Analysis Workshop 16 Rheumatoid Arthritis data.



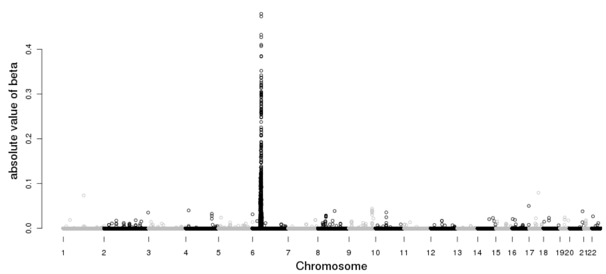
(a) SMCP

(b) LASSO

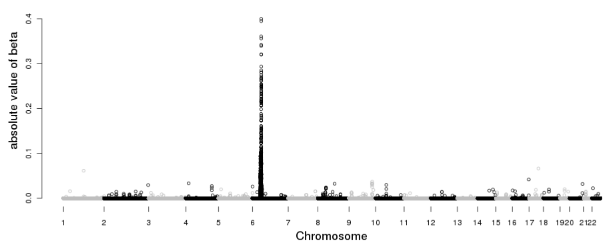
Figure 2: Plot of $-\log_{10}(p\text{-value})$ for SNPs on chromosome 6 selected by (a) the SMCP method and (b) the LASSO method for the rheumatoid arthritis data. These p-values are generated using the multi-split method. The horizontal line corresponds to significance level 0.05.



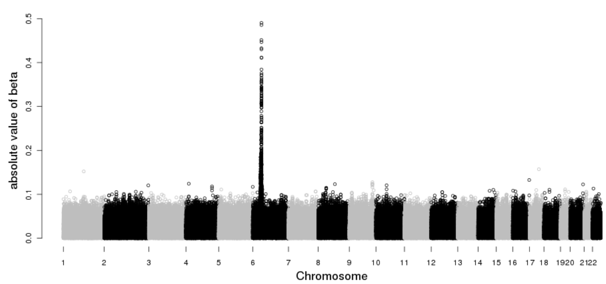
(a) SMCP



(b) MCP



(c) LASSO



(d) Regular Single-SNP Linear Regression

Figure 3: Genome-wide plot of $|\beta|$ estimates.

Table 1: Mean and standard error (in parentheses) of the number of true positive, false discovery rate (FDR) and false negative rate (FNR) over 100 simulation replications. There are 31 associated SNPs.

Method	η	True Positive	FDR	FNR
SMCP	0.05	29.12(0.78)	0.418(0.016)	0.061(0.025)
	0.06	28.75(0.87)	0.425(0.017)	0.073(0.028)
	0.08	28.24(0.81)	0.435(0.016)	0.089(0.026)
	0.1	27.87(0.75)	0.443(0.015)	0.101(0.024)
	0.2	27.02(0.67)	0.460(0.013)	0.128(0.021)
	0.3	26.14(0.45)	0.477(0.009)	0.157(0.015)
	0.4	25.97(0.36)	0.481(0.007)	0.162(0.012)
	0.5	25.71(0.61)	0.486(0.012)	0.171(0.020)
	0.6	25.42(0.61)	0.492(0.012)	0.180(0.020)
	0.7	25.15(0.56)	0.497(0.011)	0.189(0.018)
	0.8	24.82(0.55)	0.504(0.012)	0.199(0.018)
	0.9	24.66(0.65)	0.507(0.013)	0.205(0.021)
	1	24.20(0.84)	0.516(0.017)	0.219(0.027)
LASSO	—	24.31(0.83)	0.514(0.016)	0.216(0.027)

Table 2: List of SNPs selected by the SMCP and the LASSO method for a simulated data set. Recall that the 31 disease-associated SNPs are 2287 – 2298 and 2300 – 2318.

	SMCP		LASSO		Regression	
SNP	$\lvert\hat{\beta}\rvert$	p-value*	$\lvert\hat{\beta}\rvert$	p-value*	$\lvert\beta\rvert$	p-value**
2110			-0.042	1	-0.944	4.4e-04
2112			0.042	1	0.944	4.4e-04
2118	-0.001	1	-0.077	1	-0.925	2.5e-04
2120	0.002	1	0.071	1	0.920	2.7e-04
2181	-0.002	1	-0.080	1	-1.037	2.7e-04
2240	0.045	1	0.241	1	1.103	1.6e-05
2241	0.059	1	0.251	1	1.175	1.8e-05
2242	0.046	1	0.158	1	1.103	8.6e-05
2247	-0.010	1	-0.101	1	-0.941	1.7e-04
2269	-0.059	1	-0.481	1	-1.627	1.6e-06
2270	0.034	1			1.136	0.002
2272	-0.003	1	-0.089	1	-0.979	2.2e-04
2279	-0.019	1	-0.181	1	-1.506	1.3e-04
2281			-0.037	1	-1.145	5.2e-04
2284			-0.037	1	-1.310	5.5e-04
2286	-0.167	1	-0.163	1	-1.165	9.1e-05
2287	0.621	0.006	0.816	0.008	1.642	9.5e-12
2288	0.618	0.006	0.812	0.008	1.640	1.2e-11
2289	-0.896	0.324	-0.890	0.191	-2.223	1.5e-08
2290	0.467	0.002	1.040	5.1e-04	1.884	1.2e-14
2291	0.068	1			0.569	0.383
2293	0.108	0.012	0.808	0.003	1.625	9.1e-12
2294	0.083	1			0.815	0.002
2295	-0.061	0.660	-0.413	0.405	-1.299	7.0e-07
2299	-0.132	1			-0.079	0.815
2300	0.580	0.003	1.004	0.002	1.836	2.6e-14
2301	-0.782	0.003	-1.084	0.015	-2.086	8.5e-13
2302	0.687	2.7e-04	1.205	6.3e-05	2.039	1.7e-17
2303	1.221	1			0.722	1.9e-01
2304	-0.856	0.001	-1.089	1.92e-04	-1.933	2.3e-15
2305	-0.892	8.2e-06	-1.395	1.19e-05	-2.239	1.2e-20
2306	0.824	0.030	0.724	0.014	1.527	8.1e-11
2307	-0.914	0.159	-0.684	0.203	-1.709	1.5e-08
2308	0.740	1	0.429	0.705	1.328	5.7e-07
2309	0.738	1.1e-04	1.321	1.51e-05	2.182	8.3e-19
2310	-0.910	0.252	-0.853	0.133	-2.139	1.6e-08
2311	0.477	1			0.1554	0.642
2312	0.717	9.4e-04	1.390	6.30e-05	2.412	2.6e-16
2313	1.029	1	0.036	1	1.525	5.8e-04
2314	-0.762	0.019	-0.916	0.004	-1.776	1.3e-12
2315	0.786	0.019	0.916	0.004	1.776	1.3e-12
2316	-0.831	0.006	-0.960	0.006	-1.853	9.8e-13
2317	-0.757	0.251	-0.458	0.161	-1.285	1.4e-07
2318	0.986	0.001	1.393	1.03e-04	2.442	7.0e-16
2319	9.3e-05	1			0.348	0.198
2320	0.399	0.073	0.928	0.014	2.031	3.2e-10
2321	-0.388	0.066	-0.911	0.017	-2.016	4.9e-10
2332	-0.010	1	-0.133	1	-1.046	1.2e-04
2337	-0.049	1	-0.439	1	-1.733	6.1e-06
2343	0.007	1	0.133	1	1.009	1.1e-04
2346	-0.033	1	-0.310	1	-1.414	1.6e-05
2360			-0.015	1	-1.052	6.6e-04
2363	-0.020	1	-0.273	1	-1.127	8.4e-06
2371	-3.2e-04	1	-0.059	1	-0.916	3.3e-04
2772			0.035	1	0.872	4.6e-04
4421	-0.001	1	-0.077	1	-1.109	3.0e-04
4628			-4.15e-04	1	-1.013	7.8e-04

* Computed using the multi-split method.

** Single SNP analysis, not corrected for multiple testing.

*** Empty cells stand for SNPs that are not identified from the model

Table 3: Significant SNPs (p-value < 0.05) selected by the SMCP method on chromosomes other than chromosome 6.

				SMCP		LASSO	
Gene	Chr	Position	SNP name	Estimates	p-value*	Estimates	p-value*
PTPN22	1	114089610	rs2476601	-0.026	6e-05	-0.061	2e-05
RAB28	4	12775151	rs512244	0.019	0.024	0.033	0.021
TRAF1	9	120720054	rs1953126	-0.021	0.025	-0.031	0.053
TRAF1	9	120732452	rs881375	-0.030	0.014	-0.033	0.016
TRAF1	9	120769793	rs3761847	0.029	0.014	0.033	0.027
TRAF1	9	120785936	rs2900180	-0.019	0.008	-0.037	0.006
CA5A	16	86505516	rs12926841	-0.031	0.002	-0.042	0.002
RNF126P1	17	52478747	rs3213728	0.046	8e-06	0.066	1e-06
PHACTR3	20	57826397	rs1182531	0.018	0.025	0.032	0.021

* Computed using the multi-split method.