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# Separating Sparse Signals from Correlated Noise in Binary Classification

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## Abstract

Among the goals of statistical genetics is to find sparse associations of genetic data with binary phenotypes, such as heritable diseases. Often, the data are obfuscated by confounders such as age, ethnicity, or population structure. A widely appreciated modeling paradigm which corrects for such confounding relies on linear mixed models. These are linear regression models with correlated noise, where the noise covariance captures similarities between the samples. We generalize this modeling paradigm to binary classification. We thereby face the technical challenge that marginalizing over the noise leads to an intractable, high-dimensional integral. We propose a variational EM algorithm to overcome this problem, where the global model parameters are  $\ell_1$ -norm regularized, leading to a sparse solution. The genetic features that the algorithm selects are much less correlated with the first principal component of the noise covariance and therefore show much less confounding. The proposed method also outperforms Gaussian process classification and uncorrelated probit regression in terms of prediction performance. In addition, we discuss ongoing work on employing stochastic gradient MCMC for this problem class.

## 1 Introduction

Genetic association studies have emerged as an important branch of statistical genetics [1, 2]. The goal of this field is to find causal associations between high-dimensional vectors of *genotypes*, such as single nucleotide polymorphisms (SNPs), and observable outcomes or *phenotypes*. These phenotypes may be continuous or binary, an example being the outcome of a certain disease. Genetic associations

are typically sparse: only a few genes are responsible for a phenotype of interest. Finding a small number of relevant positions in the genome among ten thousands of irrelevant genes is challenging. For various complex diseases, such as bipolar disorder or type 2 diabetes [3], these sparse signals are yet largely undetected [1], which is why these missing associations have been entitled the *The Dark Matter of Genomic Associations* [4].

Genetic associations can be spurious, unreliable, and unreproducible when the data are subject to confounding [5, 6, 7]. Confounding can stem from varying experimental conditions and demographics such as age, ethnicity, or gender [8]. The perhaps most important type of confounding in statistical genetics arises due to population structure [9], as well as similarities between closely related samples [8, 10, 11]. Ignoring such confounders can often lead to spurious false positive findings that cannot be replicated on independent data [12]. Correcting for such confounding dependencies is considered one of the greatest challenges in statistical genetics [13].

A popular approach of correcting for confounding in statistical genetics is based on linear mixed models [10]. These are essentially linear regression models with multivariate noise, where the noise models relatedness between the samples as a source of confounding. These models simultaneously account for a sparse contribution from the linear weight vector, and a dense contribution from the noise which is marginalized out. This algorithm finds a sparse weight vector while automatically accounting for population stratification [5].

Although successful, linear mixed models have been restricted to the linear regression case. We generalize this modeling paradigm to the case of binary classification. Probit regression forms the basis of our approach [14], where we add an  $\ell_1$ -norm (Lasso) regularizer that guarantees that the resulting weight vectors are sparse [15]. However, in contrast to simple probit regression, the model contains a correlated multivariate noise variable that correlates the binary labels. We show that two popular methods result as limiting cases:  $\ell_1$ -norm probit regression (for uncorrelated

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noise), and Gaussian process (GP) probit classification [16] (when the linear weight vector is zero). Yet, this approach faces a technical challenge: simultaneous inference of the linear weight and the correlated noise becomes intractable in high dimensions. To solve this problem, we propose the correlated probit regression algorithm (*CPR*). This algorithm lets us separate a sparse effect from correlated noise. For the limit of very large data, we introduce a second algorithm *SG-SPR* which is amenable to data subsampling.

In an experimental study on genetic data, we show the superiority of our approach over other methods. Compared to uncorrelated probit regression, our sparse features are up to 40% less correlated with the first principal component of the noise covariance that represents the confounder. Furthermore, compared to the linear mixed model Lasso [17], probit regression, and GP classification [16], our approach yields up to 5 percentage points higher prediction accuracies. In a computer malware experiment we show that our approach generalizes beyond statistical genetics.

Our paper is organized as follows. Section 2 introduces the modeling framework. We first discuss the confounding problem in genetics and introduce two versions of our model: a simplified version based on a maximum-likelihood estimate of the noise variable, and the fully correlated model. Section 3 then contains the mathematical details of the inference procedure. In section 4 we then apply our method to extract features associated with diseases and traits from confounded genetic data. We also test our method on a data set that contains a mix of different types of malicious computer software data.

## 2 Correlated Probit Regression

We first review the problem of confounding by population structure in statistical genetics in section 2.1. In section 2.2, we review linear mixed models and introduce a corresponding model for classification. In section 2.3 we connect our approach with other models.

### 2.1 Confounding and Similarity Kernels

The problem of confounding is fundamental in statistics. A confounder is a common cause both of the genotypes and the traits. When it is unobserved, it induces spurious correlations that have no causal interpretation: we say that the genotypes and traits are *confounded* [5, 6, 7].

In statistical genetics, a major source of confounding is due to population structure [9]. Population structure implies that due to common ancestry, genes of individuals that are related co-inherit a large number of genes, making them more similar to each other, whereas the genes of people of unrelated ancestry are obtained independently, making them more dissimilar. Population structure is the root of many unwanted biases. For example, when data is col-

lected only in selected geographical areas (such as in specific hospitals), one thereby introduces a selection bias into the sample, meaning that the collected genes do not represent the overall population. This can heavily distort the prediction quality of a classifier [13].

Another problem is that people who live geographically close often share other factors, such as similar environmental factors or culture. This, in turn, can lead to similar phenotypes (such as overweight, drinking habits, or diabetes). Thus, because genes correlate with location and location may correlate with specific phenotypes, there is a resulting correlation between genes and these phenotypes that does not have a causal interpretation—another manifestation of confounding by population structure. It is an active area of research to find models that are less prone to confounding [13]. In this paper, we present such a model for the setup of binary classification.

A popular approach to correcting for confounding relies on similarity kernels, or kinship matrices [9]. Given  $n$  samples, we can construct an  $n \times n$  matrix  $K$  that quantifies the similarity between samples based on some arbitrary measure. In the case of confounding by population structure, one typically chooses  $K_{ij} = X_i^\top X_j$ , where  $X_i$  is a vector of genetic features of individual  $i$ . As  $K_{ij}$  contains the scalar products between the genetic vectors of individuals  $i$  and  $j$ , it is a sensible measure of genetic similarity. As another example, when correcting for confounding by age, then we can choose  $K$  to be a matrix that contains 1 if two individuals have the same age, and zero otherwise. Details of constructing similarity kernels can be found in [9]. Next, we explain how the similarity matrix can be used to correct for confounding.

### 2.2 The Correlated Probit Regression (CPR) Model

Our model builds on the LMM-Lasso [17], an important method of statistical genetics to limit the impact of confounding. While the LMM-Lasso relies on linear regression, we generalize this approach to the much more involved classification setup, where the target values are binary. The correlated probit model is

$$y_i = \text{sign}\left(X_i^\top w + \epsilon_i\right), \quad \epsilon = (\epsilon_1, \dots, \epsilon_n)^\top \sim \mathcal{N}(0, \Sigma). \quad (1)$$

In the special case of  $\Sigma = \mathbf{I}$ , this is just the ordinary (uncorrelated) probit model. In the following, we refer to this model as *Correlated Probit Regression* (CPR). For now, we assume that the covariance matrix  $\Sigma$  is fixed and known. In our empirical studies we use the parametrization (13) where the parameters are estimated from the data.

We now derive an objective function to find an estimate of the model parameter  $w$ . To simplify the notation, we will without loss of generality assume that *all observed binary labels  $y_i$  are 1*. The reason why this assumption is no constraint is that we can always perform a linear transfor-

mation to absorb the sign of the labels into the data matrix and noise covariance<sup>1</sup>. Thus, when working with this transformed data matrix and noise covariance, our assumption is satisfied.

The likelihood function, thus, is the probability that all transformed labels are 1. This is satisfied when  $X_i^\top w + \epsilon_i > 0$ . When integrating over all realizations of noise, the resulting (marginal) likelihood is

$$\begin{aligned} \mathbb{P}(\forall i : y_i = 1 | w) &= \mathbb{P}(\forall i : X_i^\top w + \epsilon_i > 0 | w) \\ &= \int_{\mathbb{R}_+^n} \mathcal{N}(\epsilon; X^\top w, \Sigma) d^n \epsilon. \end{aligned} \quad (2)$$

The marginal likelihood is hence an integral of the multivariate Gaussian over the positive orthant. In section 3, we will present efficient approximations of this integral. Before we get there, we further characterize the model.

Next, we turn the correlated probit model into a model for feature selection. We are interested in a point estimate of the weight vector  $w$  that is sparse, i.e. contains zeros almost everywhere. This is well motivated in statistical genetics, because generally only a small number of genes are believed to be causally associated with a phenotype such as a disease. Sparsity is achieved using the Lasso [15], where we add an  $\ell_1$ -norm regularizer to the negative marginal likelihood:

$$\mathcal{L}(w) = -\log \int_{\mathbb{R}_+^n} \mathcal{N}(\epsilon; X^\top w, \Sigma) d^n \epsilon + \lambda_0 \|w\|_1. \quad (3)$$

The fact that the noise variable  $\epsilon$  and the weight vector  $w$  have different priors or regularizations makes the model identifiable and lets us cleanly distinguish between linear effects and effects of correlated noise. It is easy to show that the objective function (3) is convex.

### 2.3 Connection to Other Models

Before we come to inference, we point out how our approach connects to other methods. When removing the probit likelihood, the model becomes the linear mixed model Lasso (LMM-Lasso) by [17], hence  $\mathbb{P}(Y|w) = \mathcal{N}(Y; X^\top w, \Sigma)$ . This model has shown to improve selection of true non-zero effects as well as prediction quality [17]. Our model is a natural extension of the model by [17] to binary outcomes, such as the disease status of a patient. As we explain in this paper, inference of our model is, however, much more challenging than in [17].

Furthermore, by construction, our model captures two limiting cases: uncorrelated probit regression and Gaussian process (GP) classification. To obtain uncorrelated probit

<sup>1</sup>To this end, we apply the transformations  $X \leftarrow \text{diag}(y)X$  and  $\Sigma \leftarrow \text{diag}(y)\Sigma\text{diag}(y)$ .

regression, we simply set the parameters  $\lambda_i = 0$  for  $i \geq 2$ , thereby eliminating the non-diagonal covariance structure. To obtain GP classification, we simply omit the fixed effect (i.e., we set  $w = 0$ ) so that our model likelihood becomes  $\mathbb{P}(Y = Y^{\text{obs}}|w) = \int_{\mathbb{R}_+^n} \mathcal{N}(\epsilon; 0, \Sigma) d^n \epsilon$ , where hence the noise variable  $\epsilon$  plays the role of the latent function  $f$  in GPs [16]. When properly trained, our model will therefore outperform both approaches in terms of accuracy. We will compare our method to all three limiting cases in the experimental part of the paper and show enhanced accuracy.

## 3 Inference Algorithms

We derive three different algorithms to do inference in the correlated probit model. We want to optimize the objective function of CPR (3). This goal comes along with two major problems:

1. The  $\ell_1$ -norm regularizer for feature selection is not differentiable everywhere.
2. The likelihood contains an intractable, high-dimensional integral.

Our first method, *CPR*, directly optimizes (3) by employing expectation propagation (EP) [18] and the alternating direction method of multipliers (ADMM) [19]. We note that other means of approximate inference, such as Markov Chain Monte-Carlo for truncated Gaussian distributions [20] are also viable options. *CPR* allows us to directly optimize the objective (3) and shows very good prediction performance (see section 4). Because this algorithm relies on approximating moments of a truncated Gaussian integral in  $n$  dimensions, it does not easily scale beyond several thousands of data points. We also propose two approximate inference methods which are amenable to data subsampling and therefore scale to very large data. The first scalable method, *CPR-MAP*, relies on a MAP-approximation of the confounder instead of marginalizing it out. Although *CPR-MAP* is very fast, its prediction performance is substantially worse than CPR, as we show experimentally. Our third proposed method, *Stochastic Gradient Correlated Probit Regression (SG-CPR)*, has the same benefits of scalability. It makes use of recent breakthroughs in scalable MCMC methods [21, 22, 23] which are stochastic gradient descent [24] and, therefore, only use parts of the data in each training step. On the downside, this method suffers from large feature space dimensionality  $d$  where mixing may become slow.

### 3.1 Algorithm 1: CPR

CPR relies on a EM-type algorithm [25]. In the outer loop (the M-step), we follow gradients to optimize the objective. Since this objective function has an  $\ell_1$ -norm regularizer, we have to split this outer optimization routine into two parts, one that optimizes the likelihood and

one that optimizes the regularizer. This is described in 3.1.1. The inner loop (the E-step) consists of computing the gradient and the Hessian of the likelihood term by means of approximate inference, which is described in Sections 3.1.2 and 3.1.3.

### 3.1.1 M-step

The  $\ell_1$ -norm in the objective function (3) prevents us from directly applying gradient based methods such as Newton's method. A solution is given by ADMM that involves a generalized objective:

$$\begin{aligned} \mathcal{L}(w, z, \eta) := & -\log \int_{\mathbb{R}_+^N} \mathcal{N}(\epsilon; X^\top w, \Sigma) d^n \epsilon + \lambda_0 \|z\|_1 \\ & + \eta^\top (w - z) + \frac{1}{2} c \|w - z\|_2^2. \end{aligned}$$

We minimize over  $w$  and  $z$  and maximize over  $\eta$ . In alternating between the minimization updates for  $w$ ,  $z$  and a gradient step in  $\eta$ , we solve the original problem [19]. While the updates for  $z$  and  $\eta$  have analytic solutions, we compute the updates for  $w$  by numerical optimization. The part of the ADMM objective  $\mathcal{L}(w, z, \eta)$  depending on  $w$ , called  $\mathcal{L}(w)$  for brevity, is effectively  $\ell_2$ -norm regularized, enabling us to compute the gradient and the Hessian. This allows us to apply Newton's Method to obtain the ADMM update in  $w$ .

### 3.1.2 E-step

The inner loop of the EM-algorithm amounts to computing the gradient and Hessian of  $\mathcal{L}(w, z, \eta)$ . These are not available in closed-form, but in terms of the first and second moment of a truncated Gaussian density.

Since computing the derivatives of the linear and quadratic term is straightforward, we focus on  $\mathcal{L}_0(w) := -\log \int_{\mathbb{R}_+^N} \mathcal{N}(\epsilon; X^\top w, \Sigma) d^n \epsilon$ , which contains the intractable integral. In the following, we use the short hand notation

$$\mu \equiv \mu(w) = X^\top w. \quad (4)$$

It is convenient to introduce the following probability distribution:

$$p(\epsilon|\mu, \Sigma) = \frac{\mathbf{1}[\epsilon \in \mathbb{R}_+^n] \mathcal{N}(\epsilon; \mu, \Sigma)}{\int_{\mathbb{R}_+^n} \mathcal{N}(\epsilon; \mu, \Sigma) d^n \epsilon}. \quad (5)$$

Above,  $\mathbf{1}[\cdot]$  is the indicator function. This is just the multivariate Gaussian, truncated and normalized to the positive orthant; we call it the *posterior* distribution. We furthermore introduce

$$\begin{aligned} \mu_p(w) &= \mathbb{E}_{p(\epsilon|\mu(w), \Sigma)} [\epsilon], \\ \Sigma_p(w) &= \mathbb{E}_{p(\epsilon|\mu(w), \Sigma)} [(\epsilon - \mu_p(w))(\epsilon - \mu_p(w))^\top]. \end{aligned} \quad (6)$$

This is just the mean and the covariance of the *truncated* multivariate Gaussian, as opposed to  $\mu, \Sigma$  which are the mean and covariance of the non-truncated Gaussian.

In the following we abbreviate  $\mu_p \equiv \mu_p(w)$  and  $\Sigma_p \equiv \Sigma_p(w)$ , and write  $\Delta\mu = \mu_p - \mu$  for the difference between the means of the posterior (the truncated Gaussian) and the un-truncated Gaussian. The gradient and Hessian of  $\mathcal{L}_0(w)$  are given by

$$\begin{aligned} \nabla_w \mathcal{L}_0(w) &= \Delta\mu \Sigma^{-1} X^\top, \\ H_0(w) &= -X[\Sigma^{-1}(\Sigma_p - \Delta\mu \Delta\mu^\top) \Sigma^{-1} - \Sigma^{-1}] X^\top. \end{aligned} \quad (7)$$

Note that the variable  $w$  enters through  $\Sigma_p(w)$  and  $\Delta\mu(w)$ . Next, we describe how we approximate the intractable expectations involved in Eq. 7.

### 3.1.3 Optimizing the Objective Function

In Eq. 7 we have expressed the gradient and Hessian of  $\mathcal{L}_0(w)$  in terms of the first and second moment of the posterior (5). The problem is that computing the moments involves intractable expectations over this distribution. We employ expectation propagation (EP) [26] to approximate these expectations. Note that also other approximate inference schemes are possible, such as variational inference or sampling methods [16].

EP approximates moments of the posterior  $p(\epsilon|\mu, \Sigma)$  in terms of a variational distribution  $q(\epsilon)$ , approximately minimizing the Kullback-Leibler divergence,

$$\begin{aligned} q^*(\epsilon|\mu_{q^*}, \Sigma_{q^*}) \\ = \arg \min_q \left( \mathbb{E}_p[\log p(\epsilon|\mu, \Sigma)] - \mathbb{E}_p[\log q(\epsilon|\mu_q, \Sigma_q)] \right). \end{aligned}$$

The variational distribution  $q^*(\epsilon)$  is an un-truncated Gaussian  $q^*(\epsilon; \mu_{q^*}, \Sigma_{q^*}) = \mathcal{N}(\epsilon; \mu_{q^*}, \Sigma_{q^*})$ , characterized by the variational parameters  $\mu_{q^*}$  and  $\Sigma_{q^*}$ . We approximate the mean and covariance of the posterior  $p$  in terms of the variational distribution,  $\mu_p \approx \mu_{q^*}$ , and  $\Sigma_p \approx \Sigma_{q^*}$ . We warm-start each gradient computation with the optimal parameters of the earlier iteration.

Algorithm 1 summarizes our procedure. We denote the expectation propagation algorithm for approximating the first and second moment of the truncated Gaussian by  $\text{EP}(\mu, \Sigma)$ . Here,  $\mu$  and  $\Sigma$  are the mean and covariance matrix of the un-truncated Gaussian. The subroutine returns the first and second moments of the truncated distributions  $\mu_q$  and  $\Sigma_q$ . When initialized with the outcomes of earlier iterations, this subroutine converges within a single EP loop.

Our algorithm thus consists of three nested loops; the outer ADMM loop, containing the Newton optimization loop for computing the update in  $w$  and the inner EP loop, which computes the moments of the posterior. We choose stopping *criterion 1* to be the convergence criterion proposed by Boyd [19] and choose *criterion 2* to be always fulfilled,

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**Algorithm 1** CPR
 

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 $X = y \circ \tilde{X}$  pre-process the data
 $\Sigma = \text{diag}(y) \tilde{\Sigma} \text{diag}(y)$ 
repeat
  get  $w^{k+1}$  by EP and Newton's Method
  initialize  $w = w^k$ 
  repeat
     $(\mu_q, \Sigma_q) \leftarrow \text{EP}(X^\top w, \Sigma)$ 
     $\Delta\mu = \mu_q - X^\top w$ 
     $g = \Delta\mu^\top \Sigma^{-1} X^\top + c(w - z^k + \eta^k)^\top$ 
     $H = X[\Sigma^{-1} - \Sigma^{-1}(\Sigma_q - \Delta\mu\Delta\mu^\top)\Sigma^{-1}]X^\top + c\mathbf{I}$ 
     $w = w - \alpha_t H^{-1} g$ 
  until criterion 2
  ADMM updates
   $w^{k+1} = w$ 
   $z^{k+1} = S_{\lambda/c}(w^{k+1} + \eta^k)$  soft thresholding
   $\eta^{k+1} = \eta^k + w^{k+1} - z^{k+1}$ 
until criterion 1
  
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i. e. we perform only one Newton optimization step in the inner loop. Our experiments showed that doing only one Newton optimization step, instead of executing until convergence, is stable and leads to great speed improvements. ADMM is known to converge even when the minimizations in the ADMM scheme are not carried out exactly (see e.g. [27]).

### 3.2 Algorithm 2: CPR-MAP

For simplicity, we consider the simplest and most widely used covariance matrix  $\Sigma$  which allows us to derive an alternative formulation of the correlated probit model<sup>2</sup>. It is a combination of diagonal noise and a linear kernel of the data matrix,

$$\Sigma = \lambda_1 \mathbf{I} + \lambda_2 X^\top X. \quad (8)$$

The linear kernel  $X^\top X$  measures similarities between genes and therefore models the effect of genetic similarity between samples due to population structure. We use the following Gaussian integral identity:

$$\begin{aligned}
 \mathcal{L}(w) &= -\log \int_{\mathbb{R}^d} \mathcal{N}(\epsilon; X^\top w, \lambda_1 \mathbf{I} + \lambda_2 X^\top X) d\epsilon + \lambda_0 \|w\|_1 \\
 &= -\log \int_{\mathbb{R}^d} \mathcal{N}(w'; 0, \lambda_2 \mathbf{I}) \int_{\mathbb{R}^d} \mathcal{N}(\epsilon; X^\top (w + w'), \lambda_1 \mathbf{I}) d\epsilon dw' \\
 &\quad + \lambda_0 \|w\|_1 \\
 &\stackrel{c}{=} \log \int_{\mathbb{R}^d} p(y, w'|w) dw' + \lambda_0 \|w\|_1, \quad (9)
 \end{aligned}$$

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<sup>2</sup>Note that the approach can be easily generalized to arbitrary covariance matrix by considering the Cholesky decomposition  $\Sigma = BB^\top$ .

where

$$p(y, w'|w) \propto \mathcal{N}(w'; 0, \lambda_2 \mathbf{I}) \prod_{i=1}^n \Phi\left(\frac{X_i^\top (w + w')}{\sqrt{\lambda_1}}\right).$$

Above,  $\Phi(\cdot)$  is the cumulative standard normal distribution function. We have introduced the new Gaussian noise variable  $w'$ . Conditioned on  $w'$ , the remaining integrals factorize over  $n$ . However, since  $w'$  is unobserved (hence marginalized out), it correlates the samples. We interpret  $w'$  as a confounder.

The simplest approximation to Eq. 9 is to substitute the integral over  $w'$  by its maximum a posteriori (MAP) value, leading to the new objective function:

$$\begin{aligned}
 \mathcal{L}(w, w') &= -\sum_{i=1}^n \log \Phi\left(\frac{X_i^\top (w + w')}{\sqrt{\lambda_1}}\right) \\
 &\quad + \frac{1}{2\lambda_2} \|w'\|_2^2 + \lambda_0 \|w\|_1. \quad (10)
 \end{aligned}$$

Under the MAP approximation, the likelihood contribution to the objective function becomes completely symmetric in  $w$  and  $w'$ : only the sum  $w + w'$  enters. The difference between the two weight vectors  $w$  and  $w'$  in this approximation is only due to the different regularizers: while  $w'$  has an  $\ell_2$ -norm regularizer and is therefore dense,  $w$  is  $\ell_1$ -norm regularized and therefore sparse.

For optimizing the MAP approximated objective function (10) jointly in  $w$  and  $w'$ , we introduce a block coordinate descent scheme alternating between updates in  $w$  and  $w'$ . For updating  $w'$  we use gradient descent, while for updating  $w$  we employ ADMM (c.f. section 3.1.1).

Note that the procedure could be made faster by using a second-order optimization method for obtaining the updates in  $w'$ .

Under the MAP approximation, every feature gets a small non-zero weight from  $w'$ , and only selected features get a stronger weight from  $w$ . The idea is that  $w'$  models the population structure, which affects all genes. In contrast, we are interested in learning the sparse weight vector  $w$ , which has a causal interpretation because it involves only a small number of features.<sup>3</sup>

The MAP approximation is computationally more convenient, but it has its limits. In the original correlated probit model in Eq. 1, we marginalize over the confounder, which is more expensive. In contrast, under the MAP approximation we optimize over  $w'$  and the the objective function factorizes over  $n$ , which means that we have broken the correlations between the samples. This comes at the cost of reduced prediction performance. Since the MAP estimate of the confounder does not capture the full information of its

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<sup>3</sup>Note that the interplay of two weight vectors is different from an elastic net regularizer.

distribution, the MAP probit model tend to generalize not as well as the (full) correlated probit model. We compare both approaches experimentally in section 4.

### 3.3 Algorithm 3: SG-CPR

A recent development in scalable Bayesian inference are stochastic gradient Monte Carlo methods. These methods approximately sample from a posterior by using only a subset of data for generating a sample and, therefore, being scalable to big datasets. This is done by using stochastic optimization to provide efficient proposals for Metropolis-Hastings algorithms with high acceptance rates. We propose two versions of *SG-CPR*, one builds on Stochastic Gradient Langevin Dynamics (SGLD) [21] and the other on Constant Stochastic Gradient Descent (c-SGD) proposed in [22].

These methods assume that the likelihood factorizes, conditioned on the global variables. Up to a constant, the log posterior is

$$\log p(\theta|y) \stackrel{c}{=} \sum_{i=1}^n \log p(y_i|\theta) + \log p(\theta).$$

Let  $\mathcal{S}$  be a set of  $S$  random indices drawn uniformly at random from the index set  $\{1, \dots, n\}$ . The stochastic gradient w.r.t. the minibatch  $\mathcal{S}$  of the log likelihood term is

$$\hat{g}_{\mathcal{S}}(\theta) = \frac{1}{S} \sum_{i \in \mathcal{S}} \nabla_{\theta} \log p(y_i|\theta).$$

SGLD and c-SGD work as follows. SGLD performs decreasing stochastic gradient step on the negative log joint distribution, but adds artificial noise to prevent convergence to the optimum. Instead, the algorithm converges to a stationary distribution, which can be shown to be the posterior [21]. Constant SGD, on the other hand, only approximates the posterior. It converges faster because it operates with constant step sizes.

The following formula summarizes the two methods:

$$\begin{aligned} \text{SGLD : } \quad \theta_{i+1} &= \theta_i + \frac{\epsilon_t}{2} \hat{g}_{\mathcal{S}}(\theta_t) + \eta_t, \quad \eta_t \sim \mathcal{N}(0, \epsilon_t), \\ \text{c-SGD : } \quad \theta_{i+1} &= \theta_i + \epsilon^* \hat{g}_{\mathcal{S}}(\theta_t), \end{aligned} \quad (11)$$

where  $\epsilon_t$  is a suitable decreasing learning rate for SGLD. For c-SGD, it was shown in [22] that the optimal constant learning rate that best approximates the posterior is  $\epsilon^* = \frac{2dS}{n\text{Tr}(\mathbb{E}[\hat{g}\hat{g}^T])}$ . This definition involves the minibatch size  $S$ , feature space dimension  $d$ , and the stochastic gradient noise covariance near the optimum,  $\mathbb{E}[\hat{g}\hat{g}^T]$ .

We now explain how SGLD and c-SGD can be used for inference in the correlated probit model. Recall that the aim is to find the MAP estimate of the model by optimizing the objective function  $\mathcal{L}(w)$  (3). In section 3.2, we introduced

an auxiliary variable  $w'$  and obtained the identity

$$\mathcal{L}(w) \stackrel{c}{=} \log \int_{\mathbb{R}^d} p(y, w'|w) dw' + \lambda_0 \|w\|_1. \quad (12)$$

The following EM-algorithm [25] can be applied to optimize  $\mathcal{L}(w)$ ,

E-step: Compute  $p(w'|y, w^{t-1})$

M-step:  $w^t = \text{argmax}_w \mathbb{E}_{p(w'|y, w^{t-1})} [\log p(y, w|w)] + \lambda_0 \|w\|_1$ ,

which involves the posterior of the confounder  $p(w'|y, w)$ . This posterior can be approximated using SGLD or c-SGD. Since this algorithm is based on stochastic gradient descent *SG-CPR* scales to hundreds of thousands data points.

## 4 Empirical Analysis and Applications

We studied the performance of our proposed methods in experiments on both artificial and real-world data. We considered the versions *CPR* (the full correlated probit model as specified in Eq. 9) and *CPR-MAP* (its MAP approximation as contained in Eq. 10). An experimental analysis of *SG-CPR* is left to future work.

Our data was taken from the domains of statistical genetics and computer malware prediction. Our achievements can be summarized as follows:

- We compare against 3 competing methods, including uncorrelated probit regression, GP classification and the LMM Lasso. In all considered cases, CPR achieves higher classification performance.
- The features that our algorithm finds are up to 40% less confounded by population structure.
- CPR outperforms its MAP approximation across all considered datasets. Yet, in many cases CPR-MAP is a cheap alternative to the full model.

### 4.1 General Experimental Setup

For the real-world and synthetic experiments, we first need to make a choice for the class of kernels that we use for the covariance matrix. We choose a combination of three contributions,

$$\Sigma = \lambda_1 \mathbf{I} + \lambda_2 X^T X + \lambda_3 \Sigma_{\text{side}}. \quad (13)$$

The third term is optional and depends on the context; it is a kernel that we extract from side information in the form of an additional feature matrix  $X'$ , where we choose  $\Sigma_{\text{side}}$  as an RBF kernel on top of the side information  $X'$ . Note that this way, the data matrix enters the model both through the linear effect but also through the linear kernel. We evaluate the methods by using  $n$  instances of the dataset for training

and splitting the remaining examples equally into validation and test sets. This process is repeated 50 times, over which we report on average accuracies or areas under the ROC curve (AUCs) as well as standard errors [28].

The hyper parameters of the kernels, together with the regularization parameter  $\lambda_0$ , were determined on the validation set, using grid search over a sufficiently large parameter space (optimal values are attained inside the grid; in most cases  $\lambda_i \in [0.1, 1000]$ ). For all datasets, the features were centered and scaled to unit standard deviation, except in experiment 4.4, where the features are binary.

In sections 4.3 and 4.4, we show that including a linear kernel into the covariance matrix leads to top features which are less correlated with the population structure in comparison to the features of uncorrelated probit regression. The correlation plots<sup>4</sup> in Fig. 4 show the mean correlation of the top features with population structure and the corresponding standard errors.

## 4.2 Simulated Data

We generate synthetic data as follows. We generate a weight vector  $w \in \mathbb{R}^{50}$  with  $1 \leq k \leq 50$  entries being 1, and the other  $50-k$  entries being 0. We then create a random covariance matrix  $\Sigma_{\text{side}} \in \mathbb{R}^{200 \times 200}$ , which serves as side information matrix<sup>5</sup>. We draw 200 points  $X = \{x_1, \dots, x_{200}\}$  independently from a uniform distribution over the unit cube  $[-1, 1]^{50}$  and create the labels according to the probit model (1), using  $\Sigma_{\text{side}}$  as covariance matrix. We reserve 100 samples for training and 50 for validation and testing, respectively. As a benchmark we introduce the *oracle classifier*, where we use the correlated probit model (with covariance matrix  $\Sigma_{\text{side}}$ ) but skip the training and instead use the true underlying  $w$  for prediction.

For several  $1 \leq k \leq 50$ , we generate a dataset according to the above described procedure. In Fig. 1, we report on the so-achieved accuracies with respect to the percentage

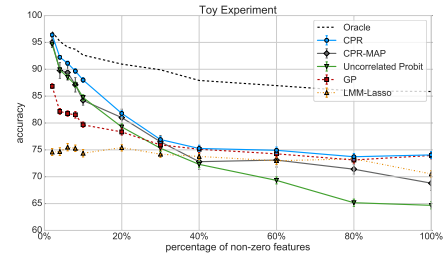
<sup>4</sup>The correlation plots in Fig. 4 are created according to [8] as follows. First, we randomly choose 70% of the available data as training set and obtain a weight vector  $w$  by training. We compute the empirical Pearson correlation coefficient

of each feature with the first principle component of the linear kernel on top of the data. This is a way to measure the correlation with the population structure [29]. We define the index set  $I$  by taking the absolute value of each entry of  $w$  and sorting them in descending order. We now sort the so-obtained list of correlation coefficients with respect to the index set  $I$  and obtain a resorted list of correlation coefficients  $(c_1, \dots, c_n)$ . In the last step, we obtain a new list  $(\hat{c}_1, \dots, \hat{c}_n)$  by smoothing the values, computing  $\hat{c}_i := \frac{1}{i} \sum_k^i c_k$ . Finally, we plot the values  $(\hat{c}_1, \dots, \hat{c}_n)$  with respect to  $I$ . This procedure was repeated 30 times for different random choices of training sets.

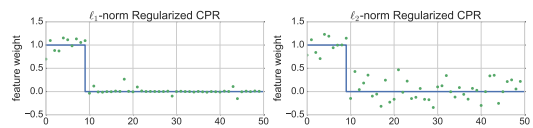
<sup>5</sup>The covariance matrix was created as follows. The random generator in MATLAB version 8.3.0.532 was initialized to `seed = 20` using the `rng(20)` command. The matrix  $\Sigma_{\text{side}}$  was realized in two steps via  $A=2*\text{rand}(50,200)-1$  and  $\Sigma_{\text{side}}=3*A'*A+0.6*\text{eye}(200)+3*\text{ones}(200,200)$ .

of non-zero features ( $\frac{k}{50}\%$ ). We observe that in the sparse scenarios ( $\leq 20\%$  non-zero features), GP classification and LMM-Lasso are clearly outperformed by CPR, achieving an accuracy up to 10 percentage points and 23 percentage points higher, respectively. Due to being  $\ell_1$ -norm regularized and therefore, having the capability of exploiting sparsity, uncorrelated probit regression performs best in this regime among the competitors, but still substantially worse than CPR. LMM-Lasso is also  $\ell_1$ -norm regularized but is not designed for a classification setting. Therefore, it cannot beat uncorrelated probit regression. In the dense scenarios, CPR outperforms LMM-Lasso (by 1 to 4 percentage points) and performs similarly well to GP classification, which also takes the correlation structure into account. In this scenario, uncorrelated probit regression is clearly worse than the other methods, because it does not take the correlation structure into account. We observe that in all scenarios the prediction performance of CPR-MAP is between uncorrelated probit regression and CPR.

In Fig. 2, we inspect the computed feature weights (green dots) of  $\ell_1$ -norm regularized and  $\ell_2$ -norm regularized CPR, respectively. The blue solid line represents the ground truth (the true underlying weight vector  $w$  with  $k = 10$  entries non-zero). We observe that the  $\ell_1$ -norm regularized probit model finds the true weights without suffering from large noise as the  $\ell_2$ -norm regularized counterpart does.



**Figure 1:** Toy: Average accuracies as a function of the number of true non-zero features in the generating model. (Proposed methods: CPR and CPR-MAP)

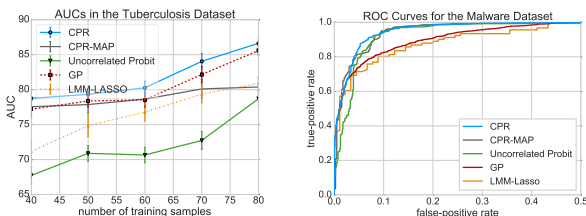


**Figure 2:** Toy: Ground truth (blue solid line) and feature weights (green dots) of  $\ell_1$ -norm (LEFT) and  $\ell_2$ -norm (RIGHT) regularized correlated probit regression.

### 4.3 Tuberculosis Disease Outcome Prediction From Gene Expression Levels

We obtained the dataset by [30] from the National Center for Biotechnology Information website<sup>6</sup>, which includes 40 blood samples from patients with active tuberculosis as well as 103 healthy controls, together with the transcriptional signature of blood samples measured in a microarray experiment with 48,803 gene expression levels, which serve as features for our purposes. Also available is the age of the subjects when the blood sample was taken, from which we compute  $\Sigma_{\text{side}}$ <sup>7</sup>. All competing methods are trained by using various training set sizes  $n \in [40, 80]$ . To be consistent with previous studies (e. g. [8]), we report on the area under the ROC curve (AUC), rather than accuracy. The results are shown in Fig. 3, left.

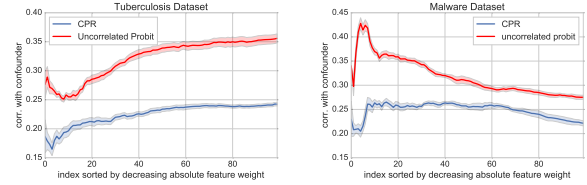
We observe that CPR achieves a consistent improvement over its uncorrelated counterpart (by up to 12 percentage points), GP classification (by up to 3 percentage points), LMM-Lasso (by up to 7 percentage points) and CPR-MAP (by up to 7 percentage points). In Fig. 4, left, we show the correlation of the top features with population structure (as confounding factor) for correlated and uncorrelated probit regression. The plot was created as explained in section 4.1. We find that the features obtained by CPR show much less correlation with population structure than the features of uncorrelated probit regression. By inspecting the correlation coefficients of the first top 10 features of both methods, we observe that the features found by CPR are 40 % less correlated with the confounder. This is because population structure was built into our model as a source of correlated noise.



**Figure 3:** LEFT, TBC: Average AUC in the tuberculosis experiment with respect to the training set size. RIGHT, MALWARE: Average ROC curves for the computer malware detection experiment.

<sup>6</sup><http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE19491>

<sup>7</sup>We compute  $\Sigma_{\text{side}}$  as RBF kernel on top of the side information age using bandwidth  $\sigma = 0.2$ .



**Figure 4:** Correlation of the of top features in the tuberculosis experiment (LEFT) and in the computer malware detection experiment (RIGHT). The x-axis is sorted by descending absolute weights.

### 4.4 Malicious Computer Software (Malware) Detection

We experiment on the Drebin dataset<sup>8</sup> [31], which contains 5,560 Android software applications from 179 different malware families. There are 545,333 binary features; each feature denotes the presence or absence of a certain source code string (such as a permission, an API call or a network address). It makes sense to look for sparse feature vector [31], as only a small number of strings are truly characteristic of a malware. The idea is that we consider populations of different families of malware when training, and hence correct for the analogue of genetic population structure in this new context, that we call “malware structure”. We concentrate on the top 10 most frequently

CPR	CPR-MAP	Uncorr. Probit	GP	LMM-Lasso
<b>74.9 ± 0.2</b>	73.1 ± 0.4	67.2 ± 0.3	69.8 ± 0.3	66.45 ± 0.3

**Table 1:**  $AUC_{0.1}$  attained on the malware dataset.

occurring malware families in the dataset.<sup>9</sup> We took 10 instances from each family, forming together a malicious set of 100 and a benign set of another 100 instances (i.e., in total 200 samples). We employ  $n = 80$  instances for training and stratify in the sense that we make sure that each training/validation/test set contains 50% benign samples and an equal amount of malware instances from each family. Since no side information is available, we only use a linear kernel and the identity matrix as components for the correlation matrix. We report on the (normalized) area under the Receiver Operating Characteristic (ROC) curve over the interval  $[0, 0.1]$  and denote this performance measure by  $AUC_{0.1}$ . In Fig. 3, right, we show the ROC curves and in Table 1 the achieved  $AUC_{0.1}$ .

We observe that correlated probit regression (CPR) achieves a consistent improvement in terms of  $AUC_{0.1}$  over its uncorrelated counterpart (by approximately 7.5 percentage points), GP classification (by approximately 5 percentage points), LMM-Lasso (by approximately 8.4 percentage

<sup>8</sup><http://user.informatik.uni-goettingen.de/~darp/drebin/download.html>

<sup>9</sup>Geinimi, FakeDoc, Kmin, Iconosys, BaseBridge, GinMaster, Opfake, Plankton, FakeInstaller, DroidKungFu.



points) and over CPR-MAP (by approximately 2 percentage points). Furthermore, in Fig. 4, right, we plot the correlation of the top features of correlated and uncorrelated probit regression with population structure. We observe that CPR leads to features, which are much less correlated with the malware structure.

#### 4.5 Flowering Time Prediction From Single Nucleotide Polymorphisms

We experiment on genotype and phenotype data consisting of 199 genetically different samples from the model plant *Arabidopsis thaliana* [32]. The genotype of each sample comprises 216,130 single nucleotide polymorphism (SNP) features. The phenotype that we aim to predict is early or late flowering of a plant when grown at ten degrees centigrade. The original dataset contains the flowering time for each of the 199 genotypes. We split the dataset into the lower and upper 45%-quantiles of the flowering time and binarized the labels, resulting in a set of 180 instances from which we use  $n = 150$  instances for training. The results

CPR	CPR-MAP	Uncorr. Probit	GP	LMM-Lasso
<b>84.1 ± 0.2</b>	83.6 ± 0.3	83.5 ± 0.2	83.6 ± 0.2	79.7 ± 0.2

**Table 2:** FLOWERING time prediction experiment (AUCs).

are reported in Table 2 and show that CPR has a slight advantage of at least 0.5 percentage points in AUC over the competitors.

An analysis restricted to the ten SNPs with largest absolute regression weights in our model showed that they lie within four well-annotated genes that all convincingly can be related to flowering, structure and growth: the gene AT2G21930 is a growth protein that is expressed during flowering, AT4G27360 is involved in microtubule motor activity, AT3G48320 is a membrane protein, involved in plant structure, and AT5G28040 is a DNA binding protein that is expressed during flowering.

## 5 Related Work

We have already commented on how our model relates to uncorrelated probit regression, GP classification, and linear mixed models. A common generalized linear model for classification is the logistic regression model [33]. Accounting for correlations in the data is non-straightforward [34]; one has to resort to approximate inference techniques, including the Laplace and mean field approximations that have been proposed in the context of GP classification [16], or the pseudo likelihood method, which has been proposed in the context of generalized linear mixed models [35]. To our knowledge feature selection has not been studied in a correlated logistic setup. On the other hand, without correlations, there is numerous work on feature se-

lection in Lasso regression [15]. Alternative sparse priors to the Lasso have been suggested in [36] for unsupervised learning (again, without compensating for confounders). The joint problem of sparse estimation in a correlated noise setup has been restricted to the linear regression case [37, 2, 17], whereas we are interested in classification. For classification, we remark that the ccSVM [8] deals with confounding in a different way and it does not yield a sparse solution. Finally, our algorithm builds on EP for GP classification [16, 26], but note that GP classification does not yield sparse estimates and, therefore, gives no insights in the underlying structure of the problem.

## 6 Conclusion

We presented a novel algorithm for sparse feature selection in binary classification where the training data show spurious correlations due to confounding. Our model is inspired by the linear mixed model of linear regression, where confounding is modeled in terms of a correlated Gaussian noise variable. While generalizing the LMM modeling paradigm to binary classification poses technical challenges as exact inference becomes intractable, our solution relies on approximate inference. We demonstrated the use of our approach on two data sets from the field of statistical genetics; a field plagued by confounding of various sorts. We showed that our algorithm finds features which are less correlated with the confounder and, therefore, lets us find a sparse signal in the data which has a causal interpretation.

Our CPR algorithm can be seen as a hybrid between an  $\ell_1$ -norm regularized probit classifier (enforcing sparsity) and a GP classifier that takes as input an arbitrary noise kernel. It distinguishes between sparse linear effects from non-sparse effects due to confounding as modeled in terms of correlated Gaussian noise. We showed that our model selects features that are less correlated with the confounders (defined as the first principal components of the noise covariance) and therefore allows to find sparse effects in the data which has a causal interpretation.

In the future, we aim to improve inference algorithm, namely the scalable version of correlated probit regression, *SG-SPR*, and provide theoretically and empirically analysis. On the other hand we plan to extend the correlated probit model. First, we want to generalize the model to a multi-class version. Second, one can use the toolbox of Gaussian process classification to automatically adjust the noise covariance from the data.

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