Nonparametric Empirical Bayes Estimation and Testing for Sparse and Heteroscedastic Signals

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Abstract
Large-scale modern data often involves estimation and testing for high-dimensional unknown parameters. It is desirable to identify the sparse signals, “the needles in the haystack”, with accuracy and false discovery control. However, the unprecedented complexity and heterogeneity in modern data structure require new machine learning tools to effectively exploit commonalities and to robustly adjust for both sparsity and heterogeneity. In addition, estimates for high-dimensional parameters often lack uncertainty quantification. In this paper, we propose a novel Spike-and-Nonparametric mixture prior (SNP) – a spike to promote the sparsity and a nonparametric structure to capture signals. In contrast to the state-of-the-art methods, the proposed methods solve the estimation and testing problem at once with several merits: 1) an accurate sparsity estimation; 2) point estimates with shrinkage/soft-thresholding property; 3) credible intervals for uncertainty quantification; 4) an optimal multiple testing procedure that controls false discovery rate. Our method exhibits promising empirical performance on both simulated data and a gene expression case study.

1 Introduction
Discovering signals in large-scale modern data is like looking for needles in the haystack – a geneticist locates genes that are associated with a disease [Efron et al., 2001, Leng et al., 2013]; a neural scientist discovers differential brain activity Perone Pacifico et al. [2004], Schwartzman et al. [2008]; a technology firm screens multiple potential innovations among thousands of A/B testings [Goldberg and Johndrow, 2017, Azevedo et al., 2020]; a personalized health system optimizes physical activities with a reinforcement learning algorithm by identifying immediate treatment effects [Liao et al., 2020]; a manager picks the superstars and underdogs among sports teams [Brown, 2008, Jiang and Zhang, 2010, Cai et al., 2019]; an economist estimates the effects of a large number of treatments [Heckman and Singer, 1984, Abadie and Kasy, 2019]. In addition, these large-scale studies often collect data from multiple sources introducing heterogeneity among units. Failing to account for both sparsity and heterogeneity will compromise both estimation and testing for the signals. In this paper, we propose a novel Spike-and-Nonparametric mixture prior (SNP) and an optimal multiple testing procedure for sparse and heteroscedastic signals estimation and testing – a spike component

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to promote sparsity and a flexible nonparametric component to capture the heterogeneous signals. The multiple testing procedure is able to control false discovery rate at desired levels and at the same time to achieve higher power.

As a motivation for our model setting, suppose we have gene expression data where each gene \( i = 1, 2, \ldots, n \) is measured among two groups, healthy subjects and cancer patients. The goal is to estimate the “true” difference in gene expression between two groups \( \mu_i \) and to test which genes are “truly” differentially expressed. It is expected that only few genes express differentially and the standard deviation of each gene expression varies. A naive approach to estimate \( \mu_i \) is to take the difference of two groups’ averages, \( y_i \), which is the maximum likelihood estimator (MLE). To perform simultaneous testing, one can scale the mean difference \( y_i \) by the pooled standard error \( \sigma_i \) and then apply a standard multiple testing procedure to \( y_i/\sigma_i \), such as Benjamini and Hochberg [1995], Storey [2002], to identify significant genes.

It turns out that, unsurprisingly, the simple MLE solution is not the best. The MLE does not borrow information from each other and we should expect there exist commonalities among \( \mu_i \). One proposal to borrow strength is to assume \( \mu_i \) follows a common prior \( \pi(\cdot) \). If we further assume \( y_i \sim p(y_i|\mu_i) \), then by the Bayes’ rule, we obtain the posterior distribution \( p(\mu_i|y_i) = p(y_i|\mu_i)p(\mu_i)/p(y_i) \). However, since \( \pi \) is a hyper-parameter and is unknown, we will estimate it by maximizing the marginal likelihood function. Robbins [1956] introduced this method and named it the empirical Bayes method. The empirical Bayes method has a long-standing reputation of optimally borrowing information, and thus the crux of our problem becomes how to adaptively incorporate sparsity and heterogeneity into our model.

**The Spike-and-Nonparametric Mixture Prior (SNP)** We now formulate the gene expression example into the canonical problem of estimating a high-dimensional mean vector from a single observation. Specifically, the observed vector \( \mathbf{y} = (y_1, y_2, \ldots, y_n)' \) satisfies
\[
y_i = \mu_i + \epsilon_i \quad \text{where} \quad \epsilon_i \sim N\left(0, \sigma_i^2\right), \quad i = 1, \ldots, n
\]
where \( \sigma = (\sigma_1, \ldots, \sigma_n) \) are known. The goal is to estimate \( \mathbf{\mu} = (\mu_1, \ldots, \mu_n)' \) with precision.

For this sparse and heteroscedastic setting, we introduce the family of Spike-and-Nonparametric mixture priors for \( \mathbf{\mu} = (\mu_1, \ldots, \mu_n)' \),
\[
\pi(\mu_i|\omega, \gamma) = \omega \psi(\mu_i|\lambda_0) + (1 - \omega)\gamma(\mu_i)
\]
where the spike \( \psi(x|\lambda_0) = \frac{\lambda_0}{2} e^{-\lambda_0|x|} \) is a Laplace (double exponential) distribution, \( \gamma(\cdot) \) is a nonparametric probability density of non-zero \( \mu_i \)'s and \( \omega, \gamma \in [0, 1] \) is the weight on the spike controlling the sparsity level. When \( \lambda_0 \to \infty \), we obtained the dirac-mass nonparametric mixture prior DNP (3) as a limiting special case of SNP (2), i.e.,
\[
\pi(\mu_i|\omega, \gamma) = \omega \delta_0(\mu_i) + (1 - \omega)\gamma(\mu_i)
\]
where the spike becomes \( \delta_0(\mu_i) \), a point mass of 1 at \( \mu_i = 0 \).

Under this broad framework with the proposed spike-and-nonparametric mixture prior, we estimate the prior distribution of the location parameter \( \mathbf{\mu} \) through an expectation-maximization (EM) algorithm [Dempster et al., 1977, Laird, 1978]. The estimated prior distribution further enables us to derive the posterior distribution given the observations, which is a powerful tool for statistical estimation and inference.

In sum, our proposed spike-and-nonparametric mixture prior has several merits.

1. **Shrinkage.** SNP inherits the shrinkage property of empirical Bayes methods for normal mean estimation. In addition, the shrinkage is multi-directional, towards zero for noises and towards their corresponding nearest centers for signals.

2. **Thresholding.** As a variant of the spike-and-slab priors, SNP is capable of adaptive thresholding to cut some estimates to be exactly zero if using posterior mode as estimator.

3. **Sparsity Adaptive.** Both the shrinkage and thresholding properties of SNP adapt to different sparsity levels.

4. **Sparsity estimation.** SNP is able to estimate the sparsity well. The estimated sparsity can be then incorporated into conservative multiple testing procedures to increase the power.
5. **Multiple testing.** SNP’s inherent adaptivity to sparsity leads us to further propose a multiple testing procedure based on the posterior. The procedure controls false discovery rate (FDR) at desired levels while achieves higher power.

6. **Bayesian credible interval.** With the entire posterior of SNP, the Bayesian mechanism further provides credible interval for uncertainty quantification.

Our work builds on a long tradition of empirical Bayes estimation and the spike-and-slab priors in Bayesian variable selection. Empirical Bayes estimators adopt the Bayesian philosophy of prior while retaining the frequentist’s optimal property of their counterparts, such as the James-Stein estimator and LASSO [James and Stein, 1961, Tibshirani, 1996, Park and Casella, 2008, Carvalho et al., 2010]. Efron [2014] and Efron et al. [2019] summarized two modelling strategies – the \( g \)-modelling that estimates the prior of \( \mu \) and the \( f \)-modelling that estimates the marginal density of \( y \). On the other hand, the family of spike-and-slab priors has been widely adopted in Bayesian variable selection. Although the structure of spike-and-slab priors is very similar to that of SNP (2), a mixture structure that consists of a spike and a slab, it is the function forms imposed on the spike and the slab that differentiate the priors, such as the parametric point-mass prior variants [George and Foster, 2000, Johnstone and Silverman, 2004, Abramovich et al., 2006] and the continuous variants [George and McCulloch, 1993, Ishwaran and Rao, 2003, Ishwaran et al., 2005, Ishwaran and George, 2011, Rockova and George, 2016, Rocková, 2018]. While the parametric mixture priors enjoy mathematical tractability and computational efficiency, the nonparametric variants show robust performance [Wand and Jones, 1994, Brown and Greenshtein, 2009, Jiang and Zhang, 2009, Raykar and Zhao, 2010, Castillo and van der Vaart, 2012].

As a simultaneous estimation strategy, it is natural to connect to the multiple testing theory Benjamini and Hochberg [1995], Benjamini et al. [2001], Storey [2002], Efron [2004], Sun and Cai [2007], Efron [2012]. The mixture structure of spike-and-slab priors has direct implications on the null and non-null groups. Literature on simultaneous inference after selection is sparse [Yekutieli, 2012, Yu and Hoff, 2018, Woody and Scott, 2018].

Most works focus on either estimation or testing. In contrast, our approach does both in a unified framework. In addition, we provide uncertainty quantification for the estimation. Note that most of the methods mentioned above focus on homoscedastic error until recent extensions to the heteroscedastic case, both for empirical Bayes estimation [Xie et al., 2012, Weinstein et al., 2018, Banerjee et al., 2020, Jiang et al., 2020] and multiple testing [Lei and Fithian, 2016, Ignatiadis et al., 2016, Fu et al., 2020]. The closest state-of-the-arts include Banerjee et al. [2020] that focuses on estimation with a nonparametric prior using the \( f \)-modelling, which is unable to estimate sparsity or provide uncertainty quantification. Jiang et al. [2020] that adopts the \( g \)-modelling with a nonparametric prior using the convex relaxation by Koenker and Mizera [2013] and Koenker and Gu [2017] instead of the EM algorithm, the spike-and-slab LASSO [Rockova and George, 2016] that imposes two Laplace distributions for the mixture prior with no nonparametric components, and Fu et al. [2020] that focuses on multiple testing adjusting for heteroscedasticity. Our method cross-fertilizes the merits of both Laplacian’s ability to capture sparsity and the nonparametric empirical Bayes \( g \)-modelling’s flexibility to model signals, and thus provides accurate sparsity estimation, signal estimation with uncertainty quantification, and an optimal multiple testing procedure.

The rest of the paper is organized as follows. Section 2 summarizes the Bayesian set up. Section 3 describes an EM algorithm to estimate the unknown hyper-parameters in the prior. The estimated hyper-parameters are then plugged in to derive the posterior and to produce point estimates and credible intervals. Section 4 focuses on the multiple hypothesis testing problem and derives an optimal FDR control procedure based on the posterior. In Section 5, our empirical results of both simulations and a gene expression case study demonstrate that our procedure adapts to sparsity and heteroscedasticity better than its counterparts. We conclude the paper with discussions in Section 6.

### 2 The Bayesian Setup

**Likelihood** The likelihood of the parameters \( \mu \) given the independent observations \( y \) can be factorized into \( L(y | \mu) = \prod_{i=1}^n p(y_i | \mu_i, \sigma) = \prod_{i=1}^n \varphi(y_i | \mu_i, \sigma) \) where \( \varphi \) is the density function for normal distribution. Note that the maximum likelihood estimator of \( \mu \) is the observation \( y \) itself. The normality assumption can be relaxed to the entire exponential family. The case of correlated \( y \) can be addressed by a two-stage procedure as described in Section 6.
We impose zero as one of the grid points and we now have all the Bayesian ingredients. Once we estimate all the unknown parameters in (6), we obtain estimates
\[
\pi(\mu_i|\omega, \gamma) = \omega \psi(\mu_i|\lambda_0) + (1-\omega)\gamma(\mu_i)
\]
as in (2). The Dirac-mass-and-Nonparametric mixture prior (DNP) replaces the Laplace distribution as a point mass at zero, i.e., \(\pi(\mu_i|\omega, \gamma) = \delta_{\mu_0}(\mu_i) + (1-\omega)\gamma(\mu_i)\) as in (3).

**Prior** Our Spike-and-Nonparametric mixture prior (SNP) consists of a Laplace distribution \(\psi(x|\lambda_0) = \frac{\lambda_0}{2}e^{-\lambda_0|x|}\) as the spike and a nonparametric probability density function \(\gamma\), i.e.,
\[
\pi(\mu_i|\omega, \gamma) = \omega \psi(\mu_i|\lambda_0) + (1-\omega)\gamma(\mu_i)
\]

In order to facilitate our EM Algorithm for the nonparametric prior estimation, we discretize the nonparametric function \(\gamma\) into \(M\) many equal-length mesh with grid points, \(\min(y) - 2 \cdot sd(y) < \tau_j < \tau_{j+1} \ldots < \tau_M < \max(y) + 2 \cdot sd(y)\), and denote \(\pi_j = \mathbb{P}(\mu_i \in [\tau_j, \tau_{j+1}])\) for \(j = 1, \ldots, M\). We impose zero as one of the grid points and \(\sum_j \pi_j = 1\).

**Posterior** We assume that each \(\mu_i\) follows independently from SNP. Given the hyper-parameter \(\omega, \lambda_0\) and \(\gamma\) of SNP, the posterior of \(\mu\) given the data \(y\) is
\[
p(\mu|y, \omega, \lambda_0, \gamma, \sigma) = \prod_{i=1}^n \varphi(y_i|\mu_i, \sigma_i)\pi(\mu_i|\omega, \lambda_0, \gamma) \frac{m(y|\omega, \lambda_0, \gamma, \sigma)}{m(y|\omega, \lambda_0, \gamma, \sigma)} \tag{4}
\]

is the marginal density of the observed \(y\). The posterior (4) can now be factorized into
\[
p(\mu|y, \omega, \lambda_0, \gamma, \sigma) = \prod_{i=1}^n p(\mu_i|y_i, \omega, \lambda_0, \gamma, \sigma_i) \tag{5}
\]

We now have all the Bayesian ingredients. Once we estimate all the unknown parameters in (6), we can produce point estimates as well as credible intervals for \(\mu_i\)'s. We also get the posterior probability of \(\mu_i\) being zero which plays the key roles in sparsity estimation and multiple testing.

### 3 Sparsity Adaptive Empirical Bayes Estimation

In this section, we present our sparsity adaptive estimation. We estimate the unknown hyper-parameters in the prior by maximizing the marginal likelihood (5). The posterior of \(\mu\) is then obtained by plugging in the estimated prior. With posterior of \(\mu\), we provide the sparsity estimation and use posterior mean or posterior mode as a point estimate of \(\mu\). Since we estimate the entire posterior of \(\mu\), the highest posterior density (HPD) or equal-tailed credible intervals for \(\mu\) can be readily constructed.

#### 3.1 Prior estimation using Expectation-Maximization Algorithm

In order to facilitate our EM Algorithm for the nonparametric prior estimation, we discretize the nonparametric function \(\gamma\) into \(M\) many equal-length mesh with grid points, \(\min(y) - 2 \cdot sd(y) < \tau_j < \tau_{j+1} \ldots < \tau_M < \max(y) + 2 \cdot sd(y)\), and denote \(\pi_j = \mathbb{P}(\mu_i \in [\tau_j, \tau_{j+1}])\) for \(j = 1, \ldots, M\). We impose zero as one of the grid points and \(\sum_j \pi_j = 1\).

**Dirac Prior** With the nonparametric function \(\gamma\) discretized, we use an EM algorithm to obtain the maximum likelihood estimate of the Dirac-Nonparametric Prior (DNP). Note the under discretization, DNP is equivalent to \(\pi(\mu_i|\pi) \sim \text{Mul}(\pi)\) where \(\pi = \{\pi_j\}_{j=1}^M\) are the hyper-parameters and \(\pi(0) = \omega\) is the sparsity. The maximum likelihood estimator maximizes the following conditional log-likelihood function of \(y\) given \(\pi\)
\[
\ell(y|\pi) = \sum_{i=1}^n \log \left\{ \sum_{j=1}^M p(y_i|\mu_j, \sigma_j^2) \pi_j \right\}. \tag{7}
\]

**Theorem 1.** Denote estimate of \(\pi\) in round \(t\) as \(\pi^{(t)}\) and define \(\pi_j^{(t)} = \frac{p(y_i|\tau_j) \pi_j^{(t)}}{\sum_{m=1}^M p(y_i|\tau_m) \pi_m^{(t)}}\). The EM algorithm updates \(\pi = (\pi_1, \ldots, \pi_M)\) by \(\pi_j^{(t+1)} = \frac{1}{n} \sum_{i=1}^n \pi_j^{(t)}\) and estimator is consistent.
Laplacian Spike Prior  As a continuum between the Dirac Mass-Nonparametric prior and Laplacian prior, SNP retains the mixture structure that consists of a Laplacian spike centered at zero, replacing the point mass, and a nonparametric portion. The maximum likelihood estimator is equivalent to solving the following optimization problem, i.e.,

\[
\arg\max_{\omega, \lambda_0, \gamma} \sum_{i=1}^{n} \log \int \varphi(y_i - \mu) \pi(\mu, \lambda_0, \gamma) d\mu
\]

(8)

where the SNP prior \(\pi(\mu | \lambda_0, \gamma) = \omega \psi(\mu | \lambda_0) + (1 - \omega) \gamma(\mu)\). For the ease of computation, we discretize the prior \(\pi(\mu | \lambda_0, \gamma)\) on the grid points. The optimization problem (8) becomes

\[
\arg\max_{\omega, \lambda_0, \gamma} \sum_{i=1}^{n} \log \left\{ \sum_{j=1}^{M} \varphi(y_i - \tau_j) \left[ \omega \psi(\tau_j | \lambda_0) + (1 - \omega) \pi_j \right] \right\}
\]

s.t. \(\sum_{j} \pi_j = 1, \quad \pi_j \geq 0, \quad \lambda_0 > 0\).

To facilitate the EM algorithm, we introduce latent variable

\[
Z \sim \text{Multi}(M, \theta)
\]

where \(\pi(Z = j) = \theta_j = \omega \psi(\tau_j) + (1 - \omega) \pi_j\). Following the EM recipe, the E-step replaces “complete-data” log-posterior by its conditional expectation with respect to \(Z\) given the observed data \(y\) and the estimate \((\omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)})\) at the \(t\) step, and then the M-step maximizes the conditional expected complete-data log-posterior with respect to \((\omega, \lambda_0, \pi)\).

To be specific, in the E-step, the conditional expectation with respect to \(Z\) given the observed data \(y\) and the estimates \((\omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)})\) is

\[
E_{Z|\omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y}[\log \pi(\omega, \lambda_0, \pi | \omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y)]
\]

\[
= \sum_{i=1}^{n} \sum_{j=1}^{M} \frac{\varphi(y_i - \tau_j) \theta_j^{(t)}}{\sum_{k} \varphi(y_i - \tau_k) \theta_k^{(t)}} \log \left( \frac{\varphi(y_i - \tau_j)}{\sum_{k} \varphi(y_i - \tau_k)} \right) + \log \left( \frac{\omega \psi(\tau_j | \lambda_0) + (1 - \omega) \pi_j}{\omega \psi(\tau_j | \lambda_0)} \right)
\]

(10)

In the M-step, we maximize the conditional expectation with respect to \((\omega, \lambda_0, \pi)\), i.e.,

\[
\arg\max_{\omega, \lambda_0, \pi} E_{Z|\omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y}[\log \pi(\omega, \lambda_0, \pi | \omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y)] \quad \text{s.t.} \quad \sum_{j} \pi_j = 1, \quad \pi_j \geq 0, \quad \lambda_0 > 0.
\]

(11)

The optimization problem can be solved by setting the partial derivatives of the Lagrangian of \(E_{Z|\omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y}[\log \pi(\omega, \lambda_0, \pi | \omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y)]\) to each parameter to zero. Denote \(\pi^{(t)}\) as

\[
E \left( Z_i = j \mid \omega^{(t)}, \lambda_0^{(t)}, \pi^{(t)}, y \right) = \sum_{j=1}^{M} \frac{\varphi(y_i - \tau_j) \theta_j^{(t)}}{\sum_{k} \varphi(y_i - \tau_k) \theta_k^{(t)}}.
\]

We obtain the analytical update step for \(\pi_j\) as

\[
\pi_j = \frac{\pi_j^{(t)} \omega + \lambda_0}{(1 - \omega) \sum_{j} \pi_j^{(t)} \omega + \lambda_0 - \omega \psi(\tau_j | \lambda_0)} \quad \text{for} \quad j = 1, \ldots, M
\]

For \(\lambda_0\) and \(\omega\), find the roots of the following equations as the solution

\[
\sum_{j=1}^{M} \pi_j \frac{\omega - \lambda_0 | \tau_j | e^{-|\lambda_0 | \tau_j}}{\omega \psi(\tau_j | \lambda_0) + (1 - \omega) \pi_j} = 0 \quad \text{and} \quad \sum_{j=1}^{M} \frac{\psi(\tau_j | \lambda_0) - \pi_j}{\omega \psi(\tau_j | \lambda_0) + (1 - \omega) \pi_j} = 0.
\]

3.2 Posterior Distribution, Estimation and Inference

For notational simplicity, we denote the estimated prior for both DNP and SNP as \(\hat{\pi}\). We obtain predictive posterior distribution by plugging in the estimated prior \(\hat{\pi}\), i.e.,

\[
\hat{p}(\mu | y_i, \hat{\pi}, \sigma_i) = \frac{\varphi(y_i | \mu, \sigma_i) \hat{\pi}(\mu)}{\hat{m}(y_i | \sigma_i)}.
\]

(12)

With the posterior distribution, we provide solutions to point estimators with credible intervals and sparsity estimation as follows.
3.2.1 Point Estimation

**Posterior Mean.** The posterior mean estimator is defined as
\[ \hat{\mu}_i = \sum_{j=1}^{M} \tau_j \hat{p}(\mu = \tau_j | y_i, \hat{\pi}, \sigma_i^2). \]
Our posterior mean estimator has a multi-directional shrinkage property, towards zero for noises induced by the spike and towards their corresponding nearest centers for signals induced by the flexible nonparametric component. Illustrated in Figure 1 as an example, the posterior mean estimator \( \hat{\mu} \times \) shrinks the observed \( y \) (○) towards its corresponding mean \( \mu \) (●), which is -5, 0 or 5 respectively.

**Posterior Mode.** The posterior mode estimator is defined as the \( \mu \) corresponding to the global mode of the posterior. The posterior mode estimator has the soft-thresholding effect that shrinks some estimates to 0 due to the spike around zero. Meanwhile, the nonparametric specification also guarantees more flexibility in capturing the data underlying structure. Illustrated in Figure 1 as an example, the two components help us achieve a better mean squared error performance, as illustrated in the numerical studies.

3.2.2 Sparsity Estimation

In the current paper, we use \( \omega \) to denote the proportion of zero \( \mu_i \)'s, through the weight in the spike-and-nonparametric prior. This sparsity \( \omega \) is an important quantity in the statistical inference. For example, in the well-known multiple testing procedures such as Benjamini and Hochberg [1995] and Storey [2002], the sparsity information is used in constructing the procedures. In practice, such sparsity information is usually unknown. A more accurate estimate of the sparsity will improve the posterior of the multiple testing procedure, as demonstrated by Benjamini et al. [2006]. We will discuss such applications in multiple testing with more details in Section 4. Focusing on the sparsity estimation itself, we propose the following sparsity estimator for DNP and SNP.

With DNP, the posterior probability of \( \mu_i = 0 \) follows immediately from the posterior distribution:

\[
\hat{p}(\mu_i = 0 | y_i, \hat{\pi}, \sigma_i^2) = \frac{p(y_i | \mu = 0, \sigma_i^2) \cdot \hat{p}(\mu = 0)}{p(y_i | \hat{\pi}, \sigma_i^2)}. \tag{13}
\]

We can then estimate the sparsity by the mean of \( \hat{\omega} = \frac{1}{n} \sum_{i=1}^{n} \hat{p}(\mu_i = 0 | y_i, \hat{\pi}, \sigma_i^2). \)

For SNP, the posterior probability of \( \mu_i = 0 \) is

\[
\hat{p}(\mu_i \in [\delta_L, \delta_R] | y_i, \hat{\pi}, \sigma_i^2) = \frac{p(y_i | \mu \in [\delta_L, \delta_R], \sigma_i^2) \cdot \hat{p}(\mu \in [\delta_L, \delta_R])}{p(y_i | \hat{\pi}, \sigma_i^2)}, \tag{14}
\]

where \( \delta_L \) and \( \delta_R \) are the intersects of two mixtures, \( \psi(\mu | \lambda_0) \) and \( \hat{\gamma}(\mu) \). Similarly, the sparsity is estimated as \( \hat{\omega} = \frac{1}{n} \sum_{i=1}^{n} \hat{p}(\mu_i \in [\delta_L, \delta_R] | y_i, \hat{\pi}, \sigma_i^2). \)

3.2.3 Credible Interval

We construct the the credible interval for \( \mu_i \) by choosing the posterior \( 1 - \alpha \) equal-tailed interval,

\[
\hat{p}(\mu_i \in [l, u] | y_i, \hat{\pi}, \sigma_i^2) = \frac{p(y_i | \mu \in [l, u], \sigma_i^2) \cdot \hat{p}(\mu \in [l, u])}{p(y_i | \hat{\pi}, \sigma_i^2)}. \tag{15}
\]

Most empirical Bayes f-modeling strategies cannot provide any uncertainty quantification by nature unless imposing parametric forms. This again shows the advantage of our prior estimation.

4 Multiple Testing

In a multiple testing framework, we want to simultaneously test

\[
H_{0i} : \mu_i = 0 \quad \text{vs.} \quad H_{1i} : \mu_i \neq 0, \quad i = 1, \ldots, m, \tag{16}
\]
for the \( m \) hypotheses. In our setting, \( m = n \) where \( n \) is the number of observations.

False Discovery Rate (FDR) was introduced by Benjamini and Hochberg [1995] and defined as the expected proportion of falsely rejected null hypotheses among all of the rejected. The classification of tested hypotheses can be summarized in Table 1. Correspondingly, \( FDR = E[\frac{Y}{\Pi}] \) is usually the main focus in the multiple testing problem, where we use \( 0/0 = 0 \) for the convenience.

There are two major testing procedures for controlling FDR based on \( p \)-values. One is to compare the \( p \)-values with a data-driven threshold as in Benjamini and Hochberg [1995]. Specifically, let \( p_{(1)} \leq p_{(2)} \leq \cdots \leq p_{(p)} \) be the ordered observed \( P \)-values of \( m \) hypotheses. Define \( k = \max \{ i : p_{(i)} \leq \frac{i\alpha}{m} \} \) and reject \( H_{(1)}^0, \ldots, H_{(k)}^0 \), where \( \alpha \) is a specified control rate. The other related approach is to find a threshold \( t \) so that the estimated FDR is no larger than \( \alpha \) [Storey, 2002]. To find a common threshold, let \( \hat{FDR}(t) = \hat{m}_0 t / (R(t) \vee 1) \), where \( R(t) \) is the number of total discoveries with the threshold \( t \) and \( \hat{m}_0 \) is an estimate of \( m_0 \). Storey [2002] first estimated \( \hat{m}_0 = (m - r(\lambda))/(1 - \lambda) \) where \( r(\lambda) = \# \{ p_{(i)} \leq \lambda \} \), then solve \( t \) such that \( \hat{FDR}(t) \leq \alpha \). The parameter \( \lambda \) can be selected by cross validation.

A related yet different strategy is to measure the likelihood of each \( \mu_i = 0 \) conditional on the test statistics – the smaller the likelihood, the more confident to reject the hypothesis. Such measure of significance is connected to optimality from a decision-theoretic perspective. Specifically, an optimal testing procedure can be constructed to minimize the objective function \( E(T) \), subject to \( R = k \) for a positive integer number \( k \). That is, given the number of total discoveries, we want to minimize the averaged number of false non-discoveries.

Suppose we consider a decision vector \( \mathbf{a} = (a_1, \ldots, a_m) \) where \( a_i = 1 \) if we reject the \( i \)-th hypothesis and \( a_i = 0 \) otherwise. A false discovery can be expressed as \( a_iI_{\mu_i = 0} \) where \( I \) is an indicator function, and similarly a false non-discovery as \( (1 - a_i)I_{\mu_i \neq 0} \). Correspondingly, the objective function can be written as

\[
\min_{(a_1, \ldots, a_m)} E \left[ \sum_{i=1}^{m} (1 - a_i)I_{\mu_i = 0} \right] \text{ s.t. } \sum_{i=1}^{m} a_i = k
\]

**Proposition 1.** Setting \( a_i = 1 \) for the smallest \( k \) of \( p(\mu_i = 0|y_i) \) obtains the optimal solution to (31).

This motivates us to consider the following multiple testing procedure: sort \( p_i \), the posterior probability of \( \mu_i \) being null in a nondecreasing order, and denote the sorted \( p_i \)'s as \( p_{(1)}, \ldots, p_{(p)} \). Then a conditional FDR given \( y \) can be expressed as

\[
\frac{E[\sum_{i=1}^{m} a_iI_{\mu_i = 0}|y]}{\sum_{i=1}^{m} a_i} = \frac{\sum_{i=1}^{m} a_i p_i}{\sum_{i=1}^{m} a_i} = \frac{1}{k} \sum_{i=1}^{k} p_{(i)}.
\]

Choose the largest \( k \) such that \( k^{-1} \sum_{i=1}^{k} p_{(i)} \leq \alpha \) for a pre-determined \( \alpha \) level. If the conditional FDR is controlled at \( \alpha \) level, the FDR is also controlled at \( \alpha \) level. It is worth mentioning that the conditional probability \( P(\mu_i = 0|y_i) \) is the local fdr as in Efron et al. [2007]. Combining with our nonparametric empirical Bayes estimate of the density function, we propose the following multiple testing procedure.

**FDR control: NEB-OPT** The non-parametric prior empirical Bayes rule for significance level \( \alpha \).

1. For each observation \( y_i \), estimate \( \hat{p}_i(y_i) \) using the estimated posterior probability of \( \mu_i = 0 \) of SNP (14) or DNP (13).

2. Order the values \( \hat{p}_i(y_i) \) computed in Step 1 from smallest to largest and denote the ordered list as \( \{\hat{p}_{(1)}, \ldots, \hat{p}_{(m)}\} \). Let \( K = \max \{ k : \sum_{j=1}^{k} \hat{p}_{(k)} / k \leq \alpha \} \). Reject the corresponding \( K \) hypotheses.

In addition to our procedure, our sparsity estimation \( \hat{\omega} \) is able to improve BH and Storey’s procedure as a better estimate of the proportion of zeros. For BH procedure, the FDR is bounded by \( \frac{m_0}{m} \alpha \)

| Number of | Number not rejected | Number rejected | Total |
|-----------|---------------------|----------------|------|
| True Null | \( U \)              | \( V \)          | \( m_0 \) |
| False Null| \( T \)              | \( S \)          | \( m_1 \) |
|           | \( m - R \)          | \( R \)          | \( m \)  |
We compare the following methods for posterior mean: 1) the generalized maximum likelihood
where $\varphi$ is various polynomial FDR levels of 1) Benjamini and Hochberg [1995] (B&H); 2) Storey et al. [2003]; 3) the SSLASSO Rockova et al. [2019] respectively.

EBayesThresh package by Johnstone and Silverman [2005], the SLOPE package by Larsson et al. [2021] and the Nonparametric Empirical Bayes Structural Tweedie (NEST) by Banerjee et al. [2020]

For sparsity estimation, we can only compare methods mentioned above that are able to estimate sparsity. Unfortunately, all the $f$-modeling approaches cannot provide sparsity estimation. Some methods estimate the sparsity as an intermediate step and we use that as the sparsity estimator.

For FDR control, we compare the empirical false discovery proportion $V/R$ and empirical power for various nominal FDR levels of 1) Benjamini and Hochberg [1995] (B&H); 2) Storey et al. [2003]; 3) Heteroscedasticity-Adjusted Ranking and Thresholding procedure (HART) of Fu et al. [2020]

Figure 2 shows the robust performance of DNP and SNP in point estimation, sparsity estimation, and credible interval coverage at different sparsity levels. In addition, SNP-OPT procedure controls FDR at various levels and increases power as expected. In the Appendix, we show that it is also the case in DNP.

5 Empirical Results

Simulated data The goal of the following design is to investigate the adaptivity of DNP and SNP to different levels of heteroscedasticity, in addition to signal strength and sparsity level. To be specific, $y_i|\mu_i \sim \mathcal{N}(\mu_i, \sigma_i)$ where $\mu_i$’s and $\sigma_i$’s are generated as follows:

$$\mu_i \overset{i.i.d.}{\sim} w_0 \delta_0 + (1-w)\mathcal{N}(1,1), \quad \sigma_i^2 \overset{i.i.d.}{\sim} U(0.5, u)$$

(19)

where $\omega \in \{0.55, 0.65, \ldots, 0.95\}$, $V \in \{1, 1.5, 2, 2.5, 3\}$ and $u \in \{1, 1.5, 2, 2.5\}$. For each setting, we set $n = 1000$ and report the above-mentioned metrics across 100 Monte Carlo repetitions. We only show $u = 1.5$ and $V = 2$ in the main text while the others are in the Appendix.1

We compare the following methods for posterior mean: 1) the generalized maximum likelihood Empirical Bayes estimator (GMLEB) of Jiang et al. [2020] using Koenker and Gu [2017]; 2) the group linear estimator by Weinstein et al. [2018]; 3) the SLOPE estimator of Bogdan et al. [2011], Su et al. [2016] with median estimator (EBayesThresh) with Laplace tails of Johnstone and Silverman [2004]; 2) the SLEP estimator of Rocková [2018]; 4) the SURE estimator (XKB.SB) and the parametric SURE estimator (XKB.M) from Xie et al. [2012]; 4) the Slab LASSO estimator of Rocková [2018]; 4) GMLEB posterior mode estimator 3.

For sparsity estimation, we can only compare methods mentioned above that are able to estimate sparsity. Unfortunately, all the $f$-modeling approaches cannot provide sparsity estimation. Some methods estimate the sparsity as an intermediate step and we use that as the sparsity estimator.

For FDR control, we compare the empirical false discovery proportion $V/R$ and empirical power for various nominal FDR levels of 1) Benjamini and Hochberg [1995] (B&H); 2) Storey et al. [2003]; 3) Heteroscedasticity-Adjusted Ranking and Thresholding procedure (HART) of Fu et al. [2020].

Figure 2 shows the robust performance of DNP and SNP in point estimation, sparsity estimation, and credible interval coverage at different sparsity levels. In addition, SNP-OPT procedure controls FDR at various levels and increases power as expected. In the Appendix, we show that it is also the case in general for various sparse, signal strength and heteroscedastic settings. Comparing DNP and SNP, the spike component of SNP demonstrates its power to capture sparsity. DNP tends to underestimate sparsity, leading to an underestimate in the posterior probability of being zero and thus DNP-OPT is over-confident in rejecting hypotheses.

Gene expression data We now apply our procedure on a prostate cancer microarray study Singh et al. [2002]1. The data consists of $N = 6, 033$ genes measured on $n = 102$ subjects, among which $n_1 = 50$ healthy controls and $n_2 = 52$ prostate cancer patients. The goal is to identify the genes that help predict prostate cancer.

1The code to reproduce all empirical results and the case study is in a Github repository (https://github.com/cccfran/SNP).

2We obtain the SURE estimator by the code adapted by Banerjee et al. [2020] from Weinstein et al. [2018] and the HART estimator by Banerjee et al. [2020].

3We obtain the EBayesThresh estimator, the SLOPE estimator and the SSLASSO estimator using the EBayesThresh package by Johnstone and Silverman [2005], the SLOPE package by Larsson et al. [2021] and the SSLASSO Rockova et al. [2019] respectively.

4We perform the Storey’s procedure with Dabney et al. [2010]. The code for HART is provided by the author.

5The microarray data is from the sda package on CRAN.
We apply BH, Storey, HART as well as our SNP-OPT and DNP-OPT to the microarray data. All procedures target FDR at level 0.05. For SNP-OPT and DNP-OPT, we simply plug in the differential difference and the pooled standard deviation estimate to our procedures. For BH and Storey, we will use the $p$-values converted from the $z$-value as $p_i = 2\Phi(-|z_i|)$ where $\Phi$ is the CDF of the standard normal distribution. HART estimates the sparsity level using Jin and Cai [2007] and provides an optional jackknifed procedure to estimate the marginal density.

BH, Storey and HART reject more hypotheses than SNP-OPT and DNP-OPT. We cannot say much since the ground truth is unknown. However, we should focus on the shape of the rejection region. As in Figure 13, the rejection regions of DNP-OPT and SNP-OPT depend on both $z_i$ and $\sigma_i$ – hypotheses correspond to large $\sigma_i$ tend not to get rejected. It worths mentioning that BH, Storey and HART are overconfident as in synthetic heteroscedastic settings. (Indeed if we adjust the empirical null as suggested in Efron [2004] to correct for the distortion using theoretical null $N(0, 1)$, they reject less hypotheses than SNP-OPT and DNP-OPT).

### 6 Summary and Discussion

In this paper, we propose a novel Spike-and-Nonparametric mixture prior (SNP) to tackle the high-dimensional sparse and heteroscedastic signal recovery problem. We develop an EM algorithm to
estimate the unknown prior and derive the posterior. With the posterior, we are able to provide both point estimates with shrinkage/thresholding property and credible intervals for uncertainty quantification. In addition, our method estimates sparsity well, more accurate than the state-of-the-art methods. Based on our posterior, we also propose an optimal multiple testing procedure controlling FDR while achieving higher power.

So far we only discuss the independent settings. However, our method can be extended to correlated settings using a two-stage procedure – we first estimate the prior ignoring correlations; and then we apply Markov chain Monte Carlo (MCMC) with Gibbs samplers to obtain the posterior.

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A Appendix

**A.1 Simulation**

The goal of the simulation is to investigate the adaptivity of DNP and SNP to different levels of signal strength, sparsity level, and heteroscedasticity. To be specific, $y_i \mid \mu_i \sim N(\mu_i, \sigma_i)$ where $\mu_i$’s and $\sigma_i$’s are generated as follows:

\[ \mu_i \overset{i.i.d.}{\sim} w \delta_0 + (1 - w) N(V, 1), \quad \sigma_i^2 \overset{i.i.d.}{\sim} U(0.5, u) \]  

where $w \in \{0.55, 0.65, \ldots, 0.95\}$, $V \in \{1, 1.5, 2, 2.5, 3\}$ and $u \in \{1, 1.5, 2, 2.5\}$. Note that $V \in \{1, 1.5, 2\}$ For each setting, we set $n = 1000$ and report the above-mentioned metrics across 100 Monte Carlo repetitions.

We compare the following metrics:

1. Relative mean Squared Error (MSE) of posterior mean $n^{-1} \sum_{i=1}^{n} (\hat{\mu}_i - \mu_i)^2$;
2. Relative mean Squared Error (MSE) of posterior mode;
3. Bias of sparsity estimation $\text{Bias}_{w_0} = \hat{\omega} - \omega$;
4. Credible interval coverage $n^{-1} \sum_{i=1}^{n} 1\{\mu \in \hat{C}I\}$;
5. Empirical FDR controlling FDR at different nominal levels;
6. Empirical power controlling FDR at 0.05 level.

Note that the relative ratio uses SNP as the base, i.e., the relative ratio is the ratio of the metric for any competing estimator to that of SNP. If the ratio is larger than 1, SNP performs better than the competing estimator.

Figure 4 reports the relative MSE of posterior mean varying the signal strength $V$, sparsity level $w$ and variance heterogeneity $u$. The columns correspond to different signal strength $V$ and the rows are across different variance heterogeneity $u$. For each plot, the x-axis is the sparsity level $w_0$ and the y-axis the ratio of the MSE of competing estimator to the MSE of SNP. We compare with 1) the generalized maximum likelihood Empirical Bayes estimator (GMLEB) of Jiang et al. [2020] using Koenker and Gu [2017]; 2) the group linear estimator by Weinstein et al. [2018];
3) the semi-parametric monotonically constrained SURE estimator (XKB.SB) and the parametric SURE estimator (XKB.M) from Xie et al. [2012]; 4) the Nonparametric Empirical Bayes Structural Tweedie (NEST) by Banerjee et al. [2020]. NEST is designed for unknown variance. We can see two clusters in terms of performance, one of the parametric methods and one of the nonparametric. The nonparametric methods perform better than the parametric counterparts. When the signal $V$ is strong, the advantages of the nonparametric methods are even larger. In general, SNP and DNP perform better than the others. The advantages is more pronounced as the sparsity level $w_0$ increases since the other methods are not specially designed for sparse data. The closest competitor with SNP and DNP is GMLEB which adapts $g$-modeling as well but does not use an EM algorithm. NEST is also comparable when the heterogeneity $u$ is relatively small.

Figure 5 reports the performance of the posterior mode estimators varying the signal strength $V$, sparsity level $w$ and variance heterogeneity $u$. We compare 1) the parametric empirical Bayes median estimator (EBayesThresh) with Laplace tails of Johnstone and Silverman [2004]; 2) the SLOPE estimator of Bogdan et al. [2011], Su et al. [2016] with $q = 0.1$; 3) the two-step Spike-and-Slab LASSO estimator of Rocková [2018]; 4) GMLEB posterior mode estimator. SNP is robust across different settings; while DNP can be less competitive since it tends to underestimate the sparsity. Comparing SNP and DNP shows the advantages of the Laplacian spike capturing sparsity. Surprisingly, our closest competitor in posterior mean estimator, GMLEB, is quite off using its posterior mode estimator. This may due to the convex relaxation Koenker and Gu [2017].

Figure 6 shows the performance of sparsity estimation $\hat{w}$ varying the signal strength $V$, sparsity level $w$ and variance heterogeneity $u$. We can only compare methods mentioned above that are able to estimate sparsity. Unfortunately, all the $f$-modeling approaches cannot provide sparsity estimation. Therefore, we only compare DNP and SNP with GMLEB, SSLASSO, EBayesThresh and HART. Note that HART uses Jin and Cai [2007] with a theoretical null $N(0, 1)$ to estimate the sparsity. SNP and DNP estimate the sparsity level with high accuracy, while DNP underestimates the sparsity when the heterogeneity $u$ is low compared to SNP. Both GMLEB and EBayesThresh underestimate the sparsity level, while HART and SSLASSO tend to overestimate. The overestimating behavior of SSLASSO agrees with Theorem 4.2 of Rocková [2018].

As a bonus of the Bayesian mechanism, we are able to provide uncertainty quantification in addition to point estimate. We construct the 95% equal-tailed credible interval from the posterior distribution. Figure 7 shows the empirical coverage and the average width of the credible interval across $w$ and $V$.
Figure 5: Posterior mode MSE relative ratio.

Figure 6: Bias of the sparsity.
Figure 7: Coverage and width of the credible interval.
Most credible intervals are overshoot while the widths of the interval are acceptable. The credible intervals are below nominal coverage when signal is weak and the heterogeneity of noise is large.

Figure 8, 9, 10 and 11 show the performance of the multiple testing procedure. Each plot is at different signal strength $V$ and different heterogeneity level $u$ or sparsity level $w$. The x-axis is the FDR control level ($\alpha$) and the y-axis is the bias of the average of the empirical ratio $V/R$ and the empirical power across 100 runs. We compare SNP-OPT and DNP-OPT with the original linear step-up Benjamini and Hochberg [1995] procedure, the pFDR of Storey [2002] and the HART procedure of Fu et al. [2020].

Figure 8 shows the empirical FDR varying the signal strength $V$ and sparsity level $w$ when the heterogeneity $u = 1.5$ across different nominal levels; while Figure 9 fixes the sparsity level $w = 0.95$ and varies the signal strength $V$ and the heterogeneity level. SNP-OPT controls false discovery rate at the desired nominal level $\alpha$, while others are overconfident and reject too many hypotheses in most of the cases. When the sparsity level is low, B&H procedure is conservative as expected. Storey’s procedure is quite robust since it estimates the error rate of a predetermined rejection region (other than the sparse setting when $w = 0.95$). It is instructive to compare DNP-OPT and SNP-OPT to see the benefits of the Laplacian spike. DNP-OPT tends to reject too many hypotheses, overshooting the nominal level $\alpha$. This is expected since DNP underestimates the sparsity level as in Figure 6. As a result, the posterior probability of being zero $\hat{p}_i(y_i)$ is underestimated. Therefore, following our NEB-OPT procedure, DNP-OPT is over-confident in rejecting hypotheses.

Similarly, Figure 10 shows the empirical power by fixing the heterogeneity level at $u = 1.5$ and varying the signal strength $V$ and sparsity level $w$ across different nominal FDR levels; while Figure 11 fixes the sparsity level $w = 0.95$ and varies the signal strength $V$ and the heterogeneity level. SNP-OPT controls FDR at nominal levels and at the same time increases power in most settings.

This concludes the simulation study. The nonparametric mixture prior is robust and versatile across various sparsity levels and signal strengths, especially for SNP. The multi-directional shrinkage property is particular desirable in the sparse set up where the noises are shrunk towards zero while the signals towards their corresponding centers. The multi-directional effect also reflects in the adaptive thresholding for the posterior mode estimator. In addition to point estimate, uncertainty quantification is readily provided from the Bayesian mechanism. The equal-tailed credible intervals show coverage at nominal level and are of reasonable widths.
Figure 9: FDR control at sparsity level $w = 0.95$.

Figure 10: Empirical power at heterogeneity level $u = 1.5$. 
With a focus on sparse data, it is desirable to have an accurate sparsity estimate. SNP is able to estimate the sparsity level by nature, and it estimates the sparsity well. It had been troubling to the authors that DNP tends to underestimate the sparsity due to the dispersion around zero. The underestimate of DNP also compromises the performance of the multiple testing procedures. Remedies such as a wider gap between zero and the grid points around zero are not adaptive and rather artificial. SNP, on the other hand, replaces the point-mass at zero with a Laplacian spike to handle the sparsity. The adaptivity of the spike component is particularly attractive.

The proposed multiple testing procedures, NEB-OPT, control FDR at nominal levels in different settings and achieve higher power.

A.2 Gene expression data

As argued in Efron [2004], a small deviation from the theoretical null $N(0, 1)$ will distort the FDR analysis, resulting in too many inappropriate rejections as in Figure 13. In order to compare our methods and other methods thoroughly, we adopt the empirical null approach in Efron [2004] to first estimate the empirical null. The estimated empirical null turns out to be $N(0, 1.09^2)$. We then obtain the new $p$-value by converting the $z$-value as $p'_i = 2\Phi'(-|Z_i|)$ where $\Phi'$ is the CDF of a $N(0, 1.09^2)$ variable. We can see that comparing Figure 12a and 12b, the histogram of $p$-value estimated from the empirical null is closer to uniform compared to that estimated from the theoretical null $N(0, 1)$.

| Storey | HART | DNP-OPT | SNP-OPT |
|--------|------|---------|---------|
| 0.93   | 0.99 | 0.91    | 0.96    |

Table 2: Sparsity level estimation

We are now ready to apply BH, Storey, HART as well as our SNP-OPT and DNP-OPT to the microarray data. All procedures target to control FDR at level 0.05. For SNP-OPT and DNP-OPT, we simply plug in the differential difference and the pooled estimate of the standard deviation to our procedures. For the others, we will use the empirical null and the adjusted $p$-values $p'_i$. Both BH and Storey use the $p$-value $p'_i$ estimated from the empirical null. HART estimates the sparsity level using Jin-Cai’s method with the empirical null $N(0, 1.09^2)$, following the procedure as in Fu et al. [2020], and adopts a jacknifed procedure to estimate the marginal density. Since SNP also
Figure 12: Figure (A) shows the histogram of the unadjusted \( p \)-value. Figure (B) shows the histogram of the adjusted \( p \)-value \( p' \)’s estimated from the empirical null \( N(0, 1.09^2) \).

Figure 13: The scatter plot of \( Z \) vs \( \sigma \). The red triangles (△) label the 13 discoveries by the BH procedure. The green circle (○) labels the 44 discoveries by DNP-OPT. The purple cross (×) labels the 19 discoveries by HART jackknifed procedure. The blue solid circle (●) label the 37 discoveries by SNP-OPT. The yellow solid triangle (▲) label the 13 discoveries by Storey’s procedure. All the procedures target FDR level at 0.05.

Table 3 provides an estimate to the sparsity, we can plug in to the HART procedure as an alternative approach to estimate the non-null proportion.

| BH | Storey | HART jk | HART jk + SNP | DNP-OPT | SNP-OPT | SNP Mode |
|----|--------|---------|--------------|---------|---------|----------|
| 13 | 13     | 19      | 29           | 44      | 37      | 59       |
| 0.22% | 0.22% | 0.31%   | 0.48%       | 0.73%   | 0.61%   | 0.98%    |

Table 3 shows the number of discoveries and Figure 13 shows the discoveries on the \( Z \) vs \( \sigma \) scatter plot controlling FDR at 0.05 level. SNP-OPT and DNP-OPT reject more hypotheses than other methods. SNP-OPT rejects 37 hypotheses and DNP-OPT rejects 44. The BH procedure is the most conservative as expected, claiming 13 discoveries. Note that if we use the unadjusted \( p \)-value from
the theoretical null, the BH procedure yields 51 discoveries, many of which could be over-confident false rejections as we see in the simulation. The Storey procedure obtains similar results. The HART procedure yields 19 discoveries while the HART variant using the sparsity estimated by SNP yields 29 discoveries.

Since we do not know the ground truth, we again cannot claim much. However, it is insightful to compare the rejection regions as in Figure 13. The reject regions for SNP-OPT and DNP-OPT depend on both $Z$ and $\sigma$. The dependency is more obvious for SNP-OPT – SNP-OPT does not reject hypothesis that corresponds to large $\sigma_i$.

| Storey | HART  | DNP-OPT | SNP-OPT |
|--------|-------|---------|---------|
| 0.93   | 0.99  | 0.91    | 0.96    |

Table 4: Sparsity level estimation

Table 4 shows the sparsity estimation. Storey’s procedure estimates the sparsity at 0.93 while the Jin-Cai procedure [Jin and Cai, 2007] used by HART estimates the sparsity at 0.99. SNP-OPT, which demonstrates the accurate sparsity estimation in the simulation, estimates 0.96, in between the two mentioned.

We also compare the posterior mode estimators. The posterior mode estimator of SNP produces 59 non-zero estimate although it does not provide guarantee for FDR control. On the other hand, SLOPE rejects 0 hypothesis when controlling FDR at 0.05 level.

Lastly, Figure 15 shows the heatmap of the discovery genes by SNP-OPT vs non-discovery genes among the cancer patients and healthy subjects. Comparing the differential expression of the significant genes (discoveries) on the left and the randomly picked from the non-discoveries on the right, we see that the difference in expression level among the the cancer patients and healthy subjects is distinguishable from the significant genes, while the difference in the non-discovery group is less obvious.
The EM algorithm update with the header labelled in green and the randomly selected group from the non-discoveries with the header labelled in grey. The two horizontal panels are the cancer patients with the side bar labelled in red and the healthy group with the side bar labelled in blue.

A.3 Proof

A.4 Proof of Theorem 1

Lemma 1. Suppose we have an estimate of $\pi^{(t)}$ in round $t$. Define

$$
\pi_{j,i}^{(t+1)} = \frac{1}{n} \sum_{i=1}^{n} \pi_{j,i}^{(t)}.
$$

The EM algorithm update $\pi$ by

$$
\pi_{j,i}^{(t+1)} = \frac{1}{n} \sum_{i=1}^{n} \pi_{j,i}^{(t)}.
$$

Proof. With no information on which $\mu_i$ each $y_i$ conditions on, we introduce an unobserved indicator variable $z_i$ that is $k$ if $y_i | z_i \sim N(\tau_k, \sigma^2)$. Note that

$$
z \sim \text{Multinomial}(M, \pi).
$$

The full likelihood function then becomes

$$
L(y \mid z, \pi) = p(y \mid z) p(z \mid \pi)
$$

$$
= \prod_{i=1}^{n} \prod_{j=1}^{M} (p(y_i \mid \tau_j) \cdot \pi_j) \cdot (z_i = j)
$$

$$
= \prod_{i=1}^{n} \prod_{j=1}^{M} (p(y_i \mid \tau_j) \cdot \pi_j) \cdot (z_i = j)
$$

Figure 15: The heatmap of the discovery genes by SNP-OPT vs non-discovery genes among the cancer patients and healthy subjects. The two vertical panels are the significant group (discoveries) with the header labelled in green and the randomly selected group from the non-discoveries with the header labelled in grey. The two horizontal panels are the cancer patients with the side bar labelled in red and the healthy group with the side bar labelled in blue.
and thus the log-likelihood
\[ \ell(y \mid z, \pi) = \sum_{i=1}^{n} \sum_{j=1}^{M} I_{\{z_i = j\}} \left( \log p(y_i \mid \tau_j) + \log \pi_j \right). \] (24)

In the E-step, we take expected value of the above likelihood function over \(z\) conditional on \(y\) and \(\pi(t)\), i.e. \(\mathbb{E}^{(t)}\) refers to averaging \(z\) over the distribution \(P(z \mid \pi(t), y)\). Given the full log-likelihood (24), the expected log posterior density is
\[ \mathbb{E}^{(t)}_{z \mid \pi(t), y} \ell(z, \pi \mid y) = \sum_{i=1}^{n} \sum_{j=1}^{M} P(Z_i = j \mid y_i, \pi(t)) \left( \log p(y_i \mid \tau_j) + \log \pi_j \right). \] (25)

For the M-step, we maximize (25) over \(\pi\). Let
\[ \pi_{j,i}^{(t)} = P(Z_i = j \mid Y_i = y_i, \pi(t)) = \frac{p(y_i \mid \tau_j)\pi_j^{(t)}}{\sum_{m=1}^{M} p(y_i \mid \tau_m)\pi_m^{(t)}} \] (26)

Since the only unknowns in (26) are \(\pi_j\)’s with the constraint of \(\sum_{j=1}^{M} \pi_j = 1\), it is a constrained optimization problem
\[ \text{argmax} \pi \sum_{i=1}^{n} \sum_{j=1}^{M} P(Z_i = j \mid y_i, \pi(t)) \left( \log p(y_i \mid \tau_j) + \log \pi_j \right) \]
subject to \(\sum_{j=1}^{M} \pi_j = 1\)

By the method of Lagrange multipliers, we find the maximizer being
\[ \pi_{j,i}^{(t+1)} = \frac{\sum_{i=1}^{n} \pi_{j,i}^{(t)}}{\sum_{k=1}^{M} \sum_{i=1}^{n} \pi_{k,i}^{(t)}} = \frac{1}{n} \sum_{i=1}^{n} \pi_{j,i}^{(t)}. \] (28)

**Proof of Theorem 1.** The general consistency of the nonparametric maximum likelihood estimator was established in Kiefer and Wolfowitz [1956]. Our setup is a special case of Example 1 in Kiefer and Wolfowitz [1956], i.e., for any \(p(y \mid \mu)\) in the exponential family, assuming if \(\pi_1\) and \(\pi_2\) are two different distributions on \(\mu\), then for at least one \(y\), \(m(y \mid \pi_1) \neq m(y \mid \pi_2)\) where \(m(y \mid \pi)\) is the marginal density of \(y\), i.e. \(m(y \mid \pi) = \int p(y \mid \mu)\pi(\mu)d\mu\).

It worths mentioning that the likelihood has a convex geometry. The functional of interest is
\[ L(\pi) = \sum_{i=1}^{n} \left\{ -\log \int p(y_i \mid \mu_i)\pi(\mu_i)d\mu_i \right\}, \] (29)
which is a sum of \(-\log(\cdot)\) of a linear functional \(\int p(y_i \mid \mu_i)\pi(\mu_i)d\mu_i\). Since \(-\log(\cdot)\) is convex and non-decreasing, \(L(\pi)\) is convex if the space of \(\pi\) is convex. This is also the case for the discretized version,
\[ L(\pi) = \sum_{i=1}^{n} \left\{ -\log \sum_{j=1}^{M} p(y_i \mid \tau_j)\pi_j \right\}. \] (30)

**A.5 Proof of Proposition 1**

Let a decision vector be \(a = (a_1, \ldots, a_m)\) where \(a_i = 1\) if we reject the \(i\)-th hypothesis and \(a_i = 0\) otherwise. A false discovery can be expressed as \(a_i I_{\mu_i = 0}\) where \(I\) is an indicator function, and similarly a false non-discovery as \((1 - a_i) I_{\mu_i \neq 0}\).

An optimal testing procedure can be constructed to minimize the objective function \(\mathbb{E}(T)\), subject to \(R = k\) for a positive integer number \(k\). That is, given the number of total discoveries, we want to
minimize the averaged number of false non-discoveries. Correspondingly, the objective function can be written as

$$\min_{(a_1, \cdots, a_m)} \mathbb{E} \left[ \sum_{i=1}^{m} (1 - a_i) I_{\mu_i \neq 0} \right] \quad \text{s.t.} \quad \sum_{i=1}^{m} a_i = k. \quad (31)$$

The expectation in (31) is over the distribution of $y$ and the prior distribution of $\mu$. It is equivalent to minimize the expectation of loss function conditional on $y$, that is, minimizing

$$\min_{(a_1, \cdots, a_m)} L(a) = \sum_{i=1}^{m} \left[ (1 - a_i) P(\mu_i \neq 0 | y) \right]$$

subject to $\sum_{i=1}^{m} a_i = k. \quad (32)$

After some algebra, (32) can be re-arranged as

$$L(a) = \sum_{i=1}^{m} (1 - P(\mu_i = 0 | y)) + \sum_{i=1}^{m} a_i [P(\mu_i = 0 | y) - 1].$$

Note that $L(a)$ is increasing when the second term is increasing. Therefore, to minimize $L(a)$ subject to $\sum_{i=1}^{m} a_i = k$, for the smallest $k$ values of $P(\mu_i = 0 | y)$, we set the corresponding $a_i = 1$, and the rest of the $a_i$’s are set as 0. The proof is now complete.