Pursuing sources of heterogeneity in modeling clustered population

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Abstract
Researchers often have to deal with heterogeneous population with mixed regression relationships, increasingly so in the era of data explosion. In such problems, when there are many candidate predictors, it is not only of interest to identify the predictors that are associated with the outcome, but also to distinguish the true sources of heterogeneity, that is, to identify the predictors that have different effects among the clusters and thus are the true contributors to the formation of the clusters. We clarify the concepts of the source of heterogeneity that account for potential scale differences of the clusters and propose a regularized finite mixture effects regression to achieve heterogeneity pursuit and feature selection simultaneously. We develop an efficient algorithm and show that our approach can achieve both estimation and selection consistency. Simulation studies further demonstrate the effectiveness of our method under various practical scenarios. Three applications are presented, namely, an imaging genetics study for linking genetic factors and brain neuroimaging traits in Alzheimer’s disease, a public health study for exploring the association between suicide risk among adolescents and their school district characteristics, and a sport analytics study for understanding how the salary levels of baseball players are associated with their performance and contractual status.

KEYWORDS
clustering, finite mixture model, generalized lasso, population heterogeneity

1 | INTRODUCTION

Regression is a fundamental statistical problem, of which a prototype is to model a response \( y \in \mathbb{R} \) as a function of a \( p \)-dimensional predictor vector \( x \). In many applications, the classical assumption that the conditional association between \( y \) and \( x \) is homogeneous in the population does not hold. Rather, their conditional association may vary across several latent sub-populations or clusters. Such population heterogeneity can be modeled by a finite mixture regression (FMR), which is capable of identifying the clusters by learning multiple models together. Since first introduced by Goldfeld and Quandt (1973), FMR has been further developed in various directions and is widely used in various fields; see, for example, Jiang and Tanner (1999), Böhning (1999), McLachlan and Peel (2004), and Chen et al. (2018).

In the era of data explosion, regression problems with a large sample size and/or a large number of variables become increasingly common, which makes the modeling
of population heterogeneity even more relevant. However, while many high-dimensional methods have been developed for mixture regression (Khalili and Chen, 2007; Städler et al., 2010; Khalili, 2011), utilizing regularization has been mainly for the purpose of variable selection, that is, to identify the predictors that are relevant to the modeling of the outcome.

In this paper, we tackle a challenging and interesting problem in the context of mixture model: to identify the predictors that are truly the sources of heterogeneity. That is, besides the selection of important predictors, we aim to further divide the selected predictors into two categories, the ones that only have common effects on the outcome and the ones that have different effects in different clusters. Being able to identify the sources of heterogeneity not only could reduce the complexity of the mixture model, but also could improve the model interpretability and enable us to gain deeper insights on the outcome-predictor association.

One important field that motivates our study is the imaging genetics with application to mental disorders such as Alzheimer’s disease. As demonstrated by twin studies (Van Cauwenberghe et al., 2016), genetic factors play an import role in Alzheimer’s disease and offers great promise for disease modeling and drug development. Compared with categorical diagnoses, neuroimaging trait has distinct advantages to capture disease etiology, and has been used in replacement of conventional clinical behavioral phenotypes in genome wide association studies (GWAS). Due to the availability of large-scale brain imaging and genetics data in landmark studies like the Alzheimer’s Disease Neuroimaging Initiative (Weiner et al., 2013), a large body of literature in imaging genetics focuses on high-dimensional modeling to identify risk genetic variants (Vounou et al., 2012; Lu et al., 2015; Zhao et al., 2019). However, a major challenge in the field that has not been well investigated is how to link the imaging-associated genetic factors to actual disease diagnosis or progression and provide meaningful interpretations. Specifically, for progressive mental illness like Alzheimer’s disease, it is critical to identify biomarkers that can predict the disease at early time. Therefore, we believe that not only there are genetic factors that impact overall disease risk, but also there are the ones that have differential impacts across some sub-groups that may be corresponding to different progressive periods/stages. Although a few attempts have been made to bridge the pathological paths among genotype, imaging, and clinical outcomes (Hao et al., 2017; Bi et al., 2017; Xu et al., 2017), to the best of our knowledge, none of the existing methods consider the heterogeneity within patient cohort or imaging endophenotype, nor are they capable to identify genetic factors that give arise disease sub-groups.

Indeed, the problem of heterogeneity pursuit is prevalent in various fields, ranging from genetics, population health, to even sports analytics. In a study on suicide risk among adolescents, we used data from the State of Connecticut to explore the association between suicide risk among 15–19 years old and the characteristics of their school districts. It is of great interest to learn whether different association patterns co-exist and whether they are due to the differences in demographic, social-economic, and/or academic factors of the school districts. In a study on major league baseball players, the goal is to find out which performance measures and contract/free agent statues of the players contributed to the formation of distinct salary mechanisms or clusters.

In this work, we propose a regularized finite mixture effects regression model to perform feature selection and identify sources of heterogeneity simultaneously. The problem is formulated using the effects model parameterization (in analogous to the formulations used in analysis of variance), that is, the effect of each predictor on the outcome is decomposed to a common effect term and a set of cluster-specific terms that are constrained to sum up to zero. We consider adaptive $\ell_1$ penalization on both the cluster-specific effect parameters and common effect parameters, which leads to the identification of the relevant variables and those with heterogeneous effects.

The model estimation is conducted via an Expectation-Maximization (EM) algorithm, in which the M step results in a linearly constrained $\ell_1$ penalized regression and is solved by a Bregman coordinate descent algorithm (Bregman, 1967; Goldstein and Osher, 2009). We show that the proposed approach can also be cast as a regularized finite mixture regression with a generalized lasso penalty; this connection facilitates our theoretical analysis in showing the estimation and selection consistency. Although we mainly focus on normal mixture model and $\ell_1$ regularization, our approach can be readily generalized to other non-Gaussian models with broad class of penalties and constraints. A user-friendly R package is developed for practitioners to apply our approach.

2 | MIXTURE EFFECTS MODEL FOR HETEROGENEITY PURSUIT

2.1 | An overview of finite mixture regression

We start with a description of the classical normal finite mixture regression (FMR). Let $y \in \mathbb{R}$ be a response/outcome variable and $x = (x_1, \ldots, x_p)^T \in \mathbb{R}^p$ be a $p$-dimensional predictor vector. In FMR with $m$
components, it is assumed that a linear regression model holds for each of the \( m \) components, that is, with probability \( \pi_j \), a random sample \((y, x)\) belongs to the \( j \)th mixture component \((j = 1, \ldots, m)\), for which we have that \( y = x^\top \mathbf{b}_j + \varepsilon_j \), where \( \mathbf{b}_j \in \mathbb{R}^p \) is a fixed and unknown coefficient vector, and \( \varepsilon_j \sim N(0, \sigma_j^2) \) with \( \sigma_j > 0 \). For the ease of notation, here the intercept term is included by setting the first element of \( \mathbf{x} \) as one. Therefore, the conditional probability density function of \( y \) given \( \mathbf{x} \) is

\[
\sum_{j=1}^m \pi_j \frac{1}{\sqrt{2\pi} \sigma_j} \exp \left\{ -\frac{(y - x^\top \mathbf{b}_j)^2}{2\sigma_j^2} \right\}, \quad (1)
\]

where \( \pi_j \)'s are the mixing probabilities satisfying \( \pi_j > 0 \), \( \sum_{j=1}^m \pi_j = 1 \). We write \((\mathbf{b}_1, \ldots, \mathbf{b}_m) = (\bar{\mathbf{b}}_1, \ldots, \bar{\mathbf{b}}_p)^\top\), where \( \bar{\mathbf{b}}_k \in \mathbb{R}^m \) collects \( m \) component-specific coefficients for the predictor \( x_k \). With finite samples, the maximum likelihood approach is often used for parameter estimation and inference in FMR, via the celebrated EM algorithm (Dempster et al., 1977) and its many variates (Meng and Rubin, 1991; 1993). Khalili and Chen (2007) were among the first to propose penalized likelihood approach for variable selection in FMR models; asymptotic properties were established in their work under the fixed \( p \), large \( n \) paradigm. Städler et al. (2010) studied \( \ell_1 \) penalized FMR and derived estimation errors bounds and selection consistency under general high-dimensional setups. Khalili and Lin (2013) further studied penalized FMR for a general family of penalty functions. Other relevant works include Wedel and DeSarbo (1995), Weruaga and Via (2015), Bai et al. (2016), and Doğru and Arslan (2017). For a comprehensive review, see, for example, Khalili (2011). The penalized FMR models have been widely applied in many real-world problems, such as gene expression analysis (Xie et al., 2008), disease progression subtyping (Gao et al., 2016), multi-species distribution modeling (Hui et al., 2015), protein clustering (Chen et al., 2018), among others.

In the above mixture setup, the variance parameters \( \sigma_j^2 \) play important roles. Unlike in regular linear regression where its single variance parameter generally can be treated as nuisance in the estimation of the regression coefficients, the variance parameters in mixture models directly impact on the scaling (thus interpretation) and estimation of the regression coefficients of the multiple mixture components, and consequently, they also affect the assessment and even the definition of “heterogeneous regression effects.” To facilitate the further discussion, we present a re-scaled version of FMR (Städler et al., 2010),

\[
\mathbf{\phi}_j = \frac{\mathbf{b}_j}{\sigma_j^2} = (\phi_{1j}, \ldots, \phi_{pj})^\top, \quad \rho_j = \sigma_j^{-1} \quad (j = 1, \ldots, m),
\]

and subsequently rewrite the conditional density in (1) as

\[
f(y \mid x, \delta) = \sum_{j=1}^m \pi_j \frac{\rho_j}{\sqrt{2\pi}} \exp \left\{ -\frac{1}{2}(\rho_j y - x^\top \mathbf{\phi}_j)^2 \right\}, \quad (2)
\]

where \( \delta = (\phi_1, \ldots, \phi_m; \pi_1, \ldots, \pi_m; \rho_1, \ldots, \rho_m) \) collects all the unknown parameters. We write

\[
\Phi = (\phi_1, \ldots, \phi_m) = (\bar{\phi}_1, \ldots, \bar{\phi}_p)^\top \in \mathbb{R}^{p \times m}, \quad \phi = \text{vec}(\Phi^\top) \in \mathbb{R}^{pm},
\]

where \( \bar{\phi}_k \in \mathbb{R}^m \) collects \( m \) component-specific regression coefficients for the predictor \( x_k \) for \( k = 1, \ldots, p \) and \( \text{vec}(\cdot) \) is the columnwise vectorization operator.

### 2.2 Sources of heterogeneity under finite mixture regression

Now let us consider predictor selection and heterogeneity pursuit. A predictor \( x_k \) is said to be relevant or important, if \( \bar{\phi}_k \neq 0 \), or equivalently, \( \tilde{\phi}_k \neq 0 \). Correspondingly, define

\[
S_R = \{ k; 1 \leq k \leq p, \tilde{\phi}_k \neq 0 \}
\]

to be the index set of all the relevant predictors, and let \( p_0 = |S_R| \) denote its size. Estimating \( S_R \) is typically the main task of a variable selection method.

We aim higher. That is, besides identifying the relevant variables, we want to also find out among them which ones actually contribute to the population heterogeneity. However, the concept of “source of heterogeneity” is not as easily defined as it appears, since the different mixture components are possibly with different scales. We consider two definitions.

**Definition 1.** A predictor \( x_k \) is said to be a source of heterogeneity, if \( \bar{\phi}_k \neq c \mathbf{1} \) for any \( c \in \mathbb{R} \).

**Definition 2.** A predictor \( x_k \) is said to be a scaled source of heterogeneity, if \( \tilde{\phi}_k \neq c \mathbf{1} \) for any \( c \in \mathbb{R} \).

Both definitions have their own merits. Definition 1 is in terms of the inequality of each raw coefficient vector \( \bar{\phi}_k \) from (1), which is simple and aims to draw a direct comparison of the raw effects of \( x_k \) in different mixture components regardless of their scales. Definition 2 is in terms of the scaled counterpart \( \tilde{\phi}_k \) in (2), and the motivation is to distinguish the heterogeneity induced by the predictors and that caused by inherent scaling differences. In other words, under the second definition, we compare the standardized effects of \( x_k \) in different mixture components after putting them on the same
scale. An analogy can be drawn from the familiar analysis of variance context: comparing the means of different groups is mostly appropriate when the groups are with the same variances. Note that the two definitions become equivalent when the component variances are equal, for example, $\sigma_1^2 = \cdots = \sigma_m^2$, which is a commonly adopted assumption in mixture regression analysis.

In this work, we shall mainly focus on Definition 2, although our methodologies can be readily modified to handle the alternative definition. Based on Definition 2, let $S_H = \{k; 1 \leq k \leq p, \tilde{\beta}_k \neq \mathbf{0}, \forall \mathbf{c} \in \mathbb{R}\}$ and $p_0 = |S_H|$. Henceforth, our objective is to recover both $S_R$ and $S_H$. This can potentially lead to a much more parsimonious and interpretable model. To see this, consider as above that in an $m$-component mixture model with $p$ predictors, there are $p_0$ relevant variables, and among those, only $p_0$ variables are sources of heterogeneity. The classical FMR fits a model with $mp$ free regression parameters, which can be infeasible when $p$ is even moderately large comparing to the sample size. Meanwhile, the best model a sparse predictor selection method can possibly produce would have $mp_0$ free regression parameters. We can do better: since only $p_0$ predictors are truly the source of heterogeneity, the best model would have only $p_0 + (m - 1)p_0$ regression parameters. The saving can be substantial when $p_0 \ll p \ll m$ is large. As an example, consider one of the simulation settings to be presented in Section 5 with $m = 3$, $p = 30$, $p_0 = 10$, and $p_0 = 3$. The classic FMR is with $mp = 90$ regression parameters, the sparse selection method can possibly reduce the number to be $m p_0 = 30$, while our method can possibly further reduce the number to $p_0 + (m - 1)p_0 = 16$ through identifying the sources of heterogeneity.

2.3 Regularized mixture effects regression

Motivated by the so-called effects-model formulation commonly used in analysis of variance models, we propose the following constrained mixture effects model formulation, to facilitate the pursuit of the sources of heterogeneity in mixture regression,

$$f(y \mid x, \theta) = \sum_{j=1}^{m} \pi_j \frac{\rho_j}{\sqrt{2\pi}} \exp \left\{ -\frac{1}{2} (\rho_j y - x^T \beta_0 - x^T \beta_j)^T \right\},$$

s.t. $\sum_{j=1}^{m} \beta_{jk} = 0, k = 1, \ldots, p, \quad (3)$

where $\beta_0 = (\beta_{01}, \ldots, \beta_{0p})^T \in \mathbb{R}^p$ collects the common effects, and $\beta_j = (\beta_{j1}, \ldots, \beta_{jp})^T \in \mathbb{R}^p, j = 1, \ldots, m$, are the coefficient vectors of cluster-specific effects. The equality constraints are necessary to ensure the identifiability of the parameters. We write

$$\mathbf{B} = (\beta_0, \beta_1, \ldots, \beta_m) = (\tilde{\beta}_1, \ldots, \tilde{\beta}_p)^T \in \mathbb{R}^{p(m+1)},$$

$$\beta = \text{vec}(\mathbf{B}^T) \in \mathbb{R}^{p(m+1)},$$

where $\tilde{\beta}_k = (\beta_{0k}, \beta_{1k}, \ldots, \beta_{mk})^T \in \mathbb{R}^{m+1}$ collects the common effect and the $m$ cluster-specific effects for predictor $x_k$. The rest of the terms are similarly defined as in (2), except that we now write $\theta = (\beta_0, \beta_1, \ldots, \beta_m; \pi_1, \ldots, \pi_m; \rho_1, \ldots, \rho_m)$ to correct all the parameters under this alternative effects-model parameterization.

Now a predictor $x_k$ is deemed to be relevant whenever $\tilde{\beta}_k \neq \mathbf{0}$. Moreover, a relevant variable is deemed to be a source of heterogeneity only if there exists a $1 \leq j \leq m$ such that $\beta_{jk} \neq 0$. As such, variable selection and heterogeneity pursuit can be achieved together through a sparse estimation of $\mathbf{B}$. With $n$ independent samples $\{(y_i, x_i); i = 1, \ldots, n\}$, we propose to conduct model estimation by maximizing a constrained penalized log-likelihood criterion,

$$\max_{\theta} \left\{ -\frac{1}{n} \sum_{i=1}^{n} \log f(y_i \mid x_i, \theta) - \sum_{k=1}^{p} n \lambda P_{\gamma}(\tilde{\beta}_k) \right\},$$

$$\quad \text{s.t.} \sum_{j=1}^{m} \beta_{jk} = 0, k = 1, \ldots, p, \quad (4)$$

where $f(y \mid x, \theta)$ is the conditional density function from (3), and $P_{\gamma}(\cdot)$ is a penalty function with $\lambda$ being its tuning parameter; we mainly focus on the $\ell_1$ penalty (Tibshirani, 1996) and its adaptive version (Zou, 2006; Huang et al., 2008), that is,

$$P_{\gamma}(\tilde{\beta}_k) = \sum_{j=0}^{m} w_j |\beta_{jk}|, \quad w_{jk} = |\tilde{\beta}_{jk}|^{-\gamma}, \quad (5)$$

where $w_{jk}$s are the adaptive weights constructed from some initial estimator $\hat{\beta}_{j,k}$, with $\gamma = 0$ corresponding to the nonadaptive version and $\gamma > 0$ the adaptive version. Apparently there are many other reasonable choices of penalty functions (Fan and Li, 2001; Khalili and Lin, 2013), but our choice of $\ell_1$ is simple, convex and yet fundamental for sparse estimation.

Interestingly, the proposed constrained sparse estimation approach can also be understood as a generalized lasso method (She, 2010; Tibshirani and Taylor, 2011) based on the unconstrained model formulation in (2). To see this,
observe that each $\hat{\beta}_k$ can be written as a function of $\tilde{\phi}_k$ as

$$\hat{\beta}_k = A\tilde{\phi}_k, \quad A = \left( \frac{1/m}{I_m - 1/mI_m} \right) \in \mathbb{R}^{(m+1)\times m},$$

where $I_m$ is the $m \times 1$ vector of all ones, $I_m$ is the $m \times m$ identity matrix, and $J_m$ is the $m \times m$ matrix of ones. Therefore, the generalized lasso criterion is expressed as

$$\max_{\hat{\theta}} \left\{ l_\lambda'(\theta) \equiv \sum_{i=1}^n \log f(y_i | x_i, \theta) - n\lambda \|W(I_p \otimes A)\phi\|_1 \right\},$$

where $f(y | x, \theta)$ is the conditional density function from (2), and $W = \text{diag}(w_{jk}) \in \mathbb{R}^{p(m+1) \times p(m+1)}$ is constructed from the adaptive weights in (5) accordingly.

**Proposition 1.** The two problems in (4) and (6) are equivalent, in the sense that

- If $\hat{\theta} = (\hat{\phi}, \hat{\pi}, \hat{\rho})$ solves (6), then $\hat{\theta} = (\hat{\beta}, \hat{\pi}, \hat{\rho})$ solves (4) where $\hat{\beta} = (I_p \otimes A)\hat{\phi}$.

- And conversely, if $\hat{\theta} = (\hat{\phi}, \hat{\pi}, \hat{\rho})$ solves (4), then $\hat{\theta} = (\hat{\phi}, \hat{\pi}, \hat{\rho})$ solves (6) where $\hat{\phi}$ is such that $\hat{\phi}_j = \hat{\beta}_0 + \hat{\beta}_j$, $j = 1, \ldots, m$.

It turns out that (4) is more convenient to use in computation, while (6) is more useful in the theoretical investigation. We also show that these penalized estimation criteria avoids the unbounded likelihood problem (McLachlan and Peel, 2004) in Web Appendix B.

### 3 \ ASYMPTOTIC PROPERTIES

The generalized lasso formulation allows us to perform the asymptotic analysis under the unconstrained mixture regression model setup given in (2). The main issue is then in dealing with the special form of the generalized lasso penalty in (6). To make things clear, we use $\theta^*$ or $\hat{\theta}^*$ to denote the true parameters. We have defined $S_R$ and $S_H$ as the sets of relevant predictors and the predictors of sources of heterogeneity, respectively. Correspondingly, define

$$S = \{i; ((I_p \otimes A)\phi^*)_i \neq 0\}.$$

Recall that $\beta^* = \text{vec}(B^{1\dagger}) = (I_p \otimes A)\phi^*$, which means that $S$ encodes the sparsity pattern of all the regression coefficients $\beta^*$ in the effects models. Then the recovery of $S_R$ and $S_H$ is immediate if $S$ can be recovered.

We consider the setup that the design is random, and the number of predictors $p$ and the number of components $m$ are considered as fixed as the sample size $n$ grows. Building on the works by Fan and Li (2001), Städler et al. (2010), and She (2010), our main results are presented in the following two theorems.

**Theorem 1** (Nonadaptive Estimator). Consider model (2) with random design, fixed $p$ and $m$. Choose $\lambda = O(n^{-1/2})$. Assume the regularity conditions (A)–(C) from Web Appendix A on the joint density of $(y, x)$ hold. Then for $\gamma = 0$, there exists a local maximizer $\hat{\theta}^*_\lambda$ of (6) such that $\sqrt{n}(\hat{\theta}^*_\lambda - \theta^* ) = O_P(1)$.

**Theorem 2** (Adaptive Estimator). Consider model (2) with random design, fixed $p$ and $m$. Choose $\sqrt{n}\lambda \rightarrow 0$, $n^{(\gamma + 1)/2} \lambda \rightarrow \infty$ as $n \rightarrow \infty$, and suppose the initial estimator in constructing the weights is $\sqrt{n}$-consistent, that is, $\sqrt{n}(\hat{\theta}^{\text{ini}}_\lambda - \theta^* ) = O_P(1)$. Assume the regularity conditions (A)–(C) from Web Appendix A on the joint density of $(y, x)$ hold. Then for any $\gamma > 0$, there exists a local maximizer $\hat{\theta}^*_{\lambda}$ of (6) such that it is $\sqrt{n}$-consistent and $P(\hat{\theta}^*_{\lambda} = S) \rightarrow 1$ as $n \rightarrow \infty$.

Theorem 1 shows that the nonadaptive estimator can achieve $\sqrt{n}$-consistency in model estimation, under typical regularity conditions on the joint density of $(y, x)$. Theorem 2 shows that the adaptive estimator, under the same conditions and with weights constructed from a consistent estimator such as the nonadaptive one in Theorem 1, can further achieve consistency in feature selection and heterogeneity pursuit.

### 4 \ COMPUTATION

We propose a generalized EM algorithm for optimizing the criterion in (4), which enjoys desirable convergence guarantee that the object function is monotone ascending along the iterations. The algorithmic structure is mostly straightforward based on the work of Städler et al. (2010), except that in the M-step we need to efficiently solve an $\ell_1$ regularized weighted least squares problem with equality constraints. A Bregman coordinate descent algorithm (Goldstein and Osher, 2009) is proposed to solve it. For tuning the number of component $m$ and the penalty parameter $\lambda$, we propose to minimize a Bayesian information criterion (BIC). To save space, the derivations of the algorithm and the details on tuning are provided in Web Appendix C.
5 | SIMULATION

We compare the following methods via simulation:

- Normal mixture regression with variable selection via lasso (Mix-L, or M1) and via adaptive lasso (Mix-AL, or M2), proposed by Städler et al. (2010).
- The proposed normal mixture effects regression with variable selection and heterogeneity pursuit via lasso (Mix-HP-L, or M3) and via adaptive lasso (Mix-HP-AL, or M4).

The sample size is set to \( n = 200 \) and the number of components is set to \( m = 3 \). The data on the predictors, \( \mathbf{x}_i \in \mathbb{R}^p \) for \( i = 1, \ldots, n \), are generated independently from multivariate normal distribution with mean \( \mathbf{0} \) and covariance matrix \( \mathbf{\Sigma} \). We consider two correlation structures, that is, the uncorrelated case with \( \mathbf{\Sigma} = \mathbf{I}_p \), and the correlated case with \( \sigma_{ij} = 0.5^{|i-j|} \), where \( \sigma_{ij} \) denotes the \((i, j)\)'s entry of \( \mathbf{\Sigma} \). We consider three predictor dimensions: \( p \in \{30, 60, 120\} \). As such, the number of free model parameters is 95, 185, and 365, respectively, being either comparable or much larger than the sample size.

In each setting, the first \( p_0 = 10 \) predictors are relevant, and among them only \( p_{00} = 3 \) predictors have scaled heterogeneous effects over different components according to Definition 2. Specifically, under the mixture effects model (3) with \( m = 3 \), the sub-vectors of the first 10 entries of the scaled coefficient vectors \( \beta_j \), denoted as \( \beta_{j0} \), \( j = 0, 1, 2, 3 \), are set as

\[
\beta_{00} = (1, 1, 1, 1, 1, 0, 0, 0, 0)^T / \sqrt{\delta},
\]

\[
[2.5 pt] \beta_{10} = (0, 0, 0, 0, 0, 0, 0, -3, 3)^T / \sqrt{\delta},
\]

\[
\beta_{20} = (0, 0, 0, 0, 0, 0, 0, -3, 3, 0)^T / \sqrt{\delta},
\]

\[
[2.5 pt] \beta_{30} = (0, 0, 0, 0, 0, 0, 0, 0, 0, 3, 0)^T / \sqrt{\delta},
\]

and the variance components are set as \( (\sigma_1^2, \sigma_2^2, \sigma_3^2)^T = \delta \times (0.1, 0.1, 0.4)^T \), where \( \delta \) controls the signal-to-noise ratio (SNR) defined as \( \text{SNR} = \sum_{j=1}^{m} \pi_j \mathbf{b}_j^T \text{cov}(\mathbf{X}) \mathbf{b}_j / \sum_{j=1}^{m} \pi_j \sigma_j^2 \), with \( \mathbf{b}_j = (\beta_{j0} + \beta_j) \times \sigma_j \), \( j = 1, \ldots, m \), being the corresponding unscaled coefficient vectors as in the mean model (1). We remark that \( \mathbf{b}_j \)'s remain the same for different \( \delta \) values, for facilitating the comparison among different SNRs. We choose \( \delta = 1/8, 1/4, 1/2, 1, 2 \), corresponding to \( \text{SNR} = 200, 100, 50, 25, 12.5 \), respectively. We set \( \pi_1 = \pi_2 = \pi_3 = 1/m \) and generate the response values by (3). We choose the tuning parameter \( \lambda \) and the number of components \( m \in \{2, 3, 4\} \) by minimizing BIC. The experiment is repeated 500 times under each setting.

The following performance measures are computed. The estimation performance for the unscaled regression coefficients \( (\beta_1, \ldots, \beta_m) \), the mixing probability \( (\pi_1, \ldots, \pi_m) \), and the variances \( (\sigma_1^2, \ldots, \sigma_m^2) \) is measured by their corresponding mean squared errors (MSE).

The variable selection performance is measured by the false positive rate (FPR) and the true positive rate (TPR) for identifying relevant predictors, and the false heterogeneity rate (FHR) for identifying predictors with heterogeneous effects. Specifically, they are defined as below:

- FPR = #falsely selected variables with no effects / #variables with no effects;
- TPR = #correctly selected variables with effects / #variables with effects;
- FHR = #falsely selected variables with heterogeneous effects / #variables with common effects.

Figure 1 displays the boxplots of mean squared errors in various simulation settings, and Table 1 shows the detailed results for \( p = 60 \) with \( \mathbf{\Sigma} = \mathbf{I}_p \). The results for \( p \in \{30, 120\} \) and for the cases of correlated predictors convey similar messages, which are provided in Web Appendix D. The findings are summarized as follows.

- As expected, in general the larger the SNR and the smaller the model dimensions, the better the performance of each method.
- Adaptive method in general leads to more accurate results in both model estimation and variable selection than its nonadaptive counterpart. The improvement can be substantial. Specifically, both Mix-HP-L and Mix-HP-AL rarely miss important variables, but the former tends to select a larger model with more irrelevant variables. Indeed, the over-selection property of \( \ell_1 \) penalization is well known.
- The proposed methods Mix-HPL and Mix-HP-AL outperform their counterparts without heterogeneity pursuit, Mix-L and Mix-AL, respectively, in most simulation setups, except that when \( \text{SNR} = 12.5 \) and \( p = 120 \), all methods suffer from very low SNR and very high dimensionality. The Mix-HP-AL has the best performance among all the competing methods; its improvement over others can be substantial especially when the signal is weak or moderate and the model dimension is high; moreover, in those relatively difficult scenarios, even Mix-HPL can outperform Mix-AL.
- We have examined settings where all relevant predictors have heterogeneous effects, for which the methods with or without heterogeneity pursuit perform similarly. We have also considered settings with unequal mixing
FIGURE 1 Boxplots of mean squared errors (in log scale) for estimating the unscaled coefficient vectors, for simulation settings with \( n = 200, p \in \{30, 60, 120\} \), and \( \Sigma = \mathbf{I}_p \), and \( \text{SNR} \in \{200, 100, 50, 25, 12.5\} \). Four methods are compared: Mix-L (M1), Mix-AL (M2), Mix-HP-L (M3), and Mix-HP-AL (M4). The \( \log(\text{MSE}) \): logarithm of mean squared errors.

probabilities, where the implications are similar; see Web Appendix D. These results clearly demonstrate the benefit of heterogeneity pursuit, as it enables the potential of identifying the most parsimonious model.

We conclude that overall the proposed heterogeneity pursuit approach with adaptive lasso (Mix-HP-AL) is preferable to both the nonadaptive counterpart Mix-HP-L and the conventional methods like Mix-L and Mix-AL. The proposed method is particularly beneficial when it is believed that only very few predictors contribute to the regression heterogeneity.

6 APPLICATIONS

6.1 Alzheimer’s disease neuroimaging initiative

We performed imaging genetics analysis based on data from the Alzheimer’s disease neuroimaging initiative (ADNI) database that is a public–private partnership to study the progression of mild cognitive impairment and early Alzheimer’s disease based on different data sources including genetics, neuroimaging, and clinical assessments. (See ADNI for detailed study design and data collection information). Our goal here is to find out whether distinct clusters of disease-gene associations exist, possibly corresponding the disease stages, and to identify common genetic factors associated with overall disease risk, as well as cluster-specific ones.

Briefly, to control data quality and reduce population stratification effect, we only include 760 Caucasian subjects in this analysis. For each subject, single nucleotide polymorphisms (SNPs) genotyping data were acquired by Human 610-Quad BeadChip (Illumina, Inc., San Diego, CA) according to the manufacturer’s protocols; and raw MRI data were collected through 1.5 Tesla MRI scanners and then preprocessed by standard steps including anterior commissure and posterior commissure correction, skull-stripping, cerebellum removing, intensity inhomogeneity correction, segmentation, and registration (Shen and Davatzikos, 2004). The preprocessed brain images were further labeled regionally by existing template and then transferred following the deformable registration of subject images (Wang et al., 2011), which eventually led to 93 regions of interest over whole brain. After removing the ones with sex check failure, more than 10% missing SNPs and outliers, 741 subjects including 174 Alzheimer’s disease, 362 mild cognitive impairment, and 205 healthy controls remain in the analysis.
We consider the following imaging phenotypes: two global brain measurements, that is, whole brain/white matter volumes, and two Alzheimer’s disease related endophenotypes, that is, left and right lateral ventricles volumes. For each imaging trait, we include both SNPs belonging to the top 10 Alzheimer’s disease candidate genes provided by the AlzGene database (http://www.alzgene.org) and those identified from United Kingdom Biobank (Zhao et al., 2019) (~20,000 subjects) under the same imaging phenotype. The final list of SNP names are provided in supplementary materials. We fit our proposed Mix-AL-HP model for each imaging trait and its corresponding genetic predictors to examine the cluster patterns and select risk factors that impact the whole cohort with common effects and those impact the sub-groups/clusters heterogeneously. Age, gender, and the top five genetic principal components are always included in the models as controls with common effects and no regularization. We fit models with different component numbers ($m \in \{1, 2, \ldots, 5\}$) and with/without the assumption of equal variance; the best model is selected based by BIC.

We first examine the identified clusters for each imaging trait to see whether the cluster pattern is associated with disease progression. The numbers of clusters for the four imaging traits, left/right ventricles and whole brain/white matter volumes are 2, 3, 3, 1 with the smallest BIC values regarding $\lambda$ being 1873.12, 1871.58, 1794.04, and 2144.72, respectively. And among the three imaging traits with more than one identified cluster, the average values of imaging phenotype are shown to be clearly different over different clusters. See Web Figure 2 in Web Appendix E, which shows the cluster-specific boxplots of each imaging trait. Intriguingly, given the fact that the size of brain increases along Alzheimer’s disease progression, we are able to clearly align the identified clusters to different disease stages in light of the average volume of imaging traits. Note that for the white matter volume, which is a global brain phenotype, no cluster pattern is detected, which is biologically reasonable due to its weaker pathological bounding to disease etiology.

All the selected SNPs and their types of effect (common or cluster-specific) are summarized in Figure 2. Most of the identified genetic risk variants (e.g., SNPs within genes CD2AP, MRVII, GNAI2) associated with two Alzheimer’s disease imaging biomarkers are consistent and subtype-related, indicating the existence of varying genetic effects on brain structure over disease progression. Meanwhile, the selected SNPs related to global brain phenotypes are
**FIGURE 2** ADNI study: effects of selected SNPs and their associated genes for the four imaging phenotypes. Light color means an SNP has only common effect across clusters; Dark color means an SNP has different effects across clusters and thus is considered as a source of heterogeneity. The SNPs are ordered based on their positions on chromosomes. This figure appears in color in the electronic version of this article, and any mention of color refers to that version.

generally with common effect; again, this is due to their weaker pathological bounding to disease etiology compared with the Alzheimer’s disease related endophenotypes.

Figure 3 provides a visualization of the estimated coefficients of each selected SNP under different clusters. Based on Figure 3, we successfully detect a few SNPs showing a particular strong impact on early to middle stage Alzheimer’s disease including rs2025935, rs798532, and rs798532 located in genes BIN1, MS4A4E, and GNA12. Among them, BIN1 is the key molecular factor to modulate tau pathology and has recently been recognized as an important risk locus for late-onset Alzheimer’s disease (Tan et al., 2013); MS4A4E has been detected by GWAS as a genetic risk factor for Alzheimer’s disease based on Alzheimer’s Disease Genetic Consortium (Hollingworth et al., 2011); and GNA12, though has not been extensively reported in existing experiments, is known to over-express in human brain. Due to a typical small/moderate effect of single genetic signal, some of these variants are highly likely to be buried under existing methods without clustering overall heterogeneity. Moreover, our results provide valuable insights to prioritize future early therapeutic strategies even among all the Alzheimer’s disease genotypes. In terms of other selected SNPs, most of them have been recognized as Alzheimer’s disease risk factors in previous experiments or analyses, and they either show a common effect across all the clusters or a
mixing one including both early and late stages in our results. Detailed estimation results are reported in Web Appendix E.

6.2 Connecticut adolescent suicide risk study

Suicide among youth is a serious public health problem in the United States. The Centers for Disease Control reported that suicide is the third-leading cause of death of youth aged 15–24 based on 2013 data, and more alarmingly there has been an increasing trend over time. Suicide prevention among youth is a very challenging task, which requires a systematic approach through developing reliable metrics for assessing suicide risk, locating areas of greater risk for effective resource allocation, identifying important risk factors, among others.

We use data from the State of Connecticut at the school district level to explore the association between suicide risk among 15–19 years old and the characteristics of their school district. Specifically, the overall suicide risk of the 15–19 age group within each school district is proxied by its log-transformed 5-year average rate of inpatient hospitalizations due to suicide attempts from 2010 to 2014 (per year per 10,000 population). Several characteristics of the \( n = 119 \) school district characteristics were collected in the same period: (1) demographic measures, including percent of households that included an adult male, average household size, percent of the population that are under 18 years of age, percent of population who are White; (2) academic measures, including average score on the Connecticut
Academic Performance Test, graduation rate, dropout rate, and attendance rate of high schools in the district; (3) behavioral measures, including incidence rate, defined as the ratio between the number of disciplinary incidences and the total enrollment, and serious incidence rate; (4) economic measures, including median income and free lunch rate. More details about the data can be found in Chen and Aseltine (2017).

In the previous study, a generalized mixed-effects model was used to estimate the common effects of the school district characteristics on the suicide risk (through fixed-effects terms) and identify the “overachievers” and “underachievers” (through district-level random effects) among school districts. (It was also shown that there was no significant spatial effect.) Indeed, the existence of these anomalous school districts suggests that the regression association may not be homogeneous, and thus it is interesting to see whether additional insights can be gained by a mixture regression analysis, to reveal the potentially heterogeneous association structure, cluster the school districts, and identify the district characteristics that drive the heterogeneity. We thus apply our proposed Mix-HP-AL method to analyze the data. For dealing with the highly correlated school district measurements, we perform group-wise principal component analysis and use each leading factor to summarize the information of each category, which results in $p = 4$ district factors; the details of the principal component analysis results are provided in Web Appendix F.

Table 2 reports the estimation results, and Figure 4 shows the corresponding cluster pattern of the school districts using the naive Bayes classification rule with the estimated component probabilities $\hat{p}_{j}$, that is, $\hat{z}_{ik} = 1$ if $k = \arg\max_{j} \hat{p}_{j}$. A three-component model is selected based on the BIC, in which the three factors differentiate school districts not in terms of their overall suicide risk as we did in our prior analysis, but in terms of the association between the risk factors and suicide risk. In Table 2, one can see that only the demographic and academic factors are selected; when conditioning on the selected factors, the economic factor and the behavior factor are no longer related to the suicide risk, which may be partly due to the fact that the four factors are still moderately correlated. The major difference among the three clusters of communities involves the direction of effects of the demographic factor, which indicates a great deal of heterogeneity in how this factor impact suicide risk across communities. The majority of the school districts are in cluster 3, in which the suicide risk is negatively associated with the demographic factor; that is, in general, the larger the household size, the greater percentage of households with an adult male, the greater the proportion of population under age 18, and higher the proportion of White residents are associated with lower suicide risk, after adjusting for the effect of academic performance. In contrast, in cluster 1 the association between the suicide risk and the demographic factor is positive, such that higher rates of male householders, larger household size, higher proportions of children under 18, and a higher proportion of White residents are associated with higher suicide risk. Further analysis reveals that the 12 school districts in cluster 1 have significantly lower mean suicide risk than those in cluster 3; this suggests that the impact of the demographic factors on suicide risk may change and even flip sign with the mean suicide risk level itself. It is possible that this is caused by some “unmeasured” factors confounded with the demographic factor. Cluster 2 is the smallest in size among the three, consisting of “Regional 19” (near the University of Connecticut), “New London,” and “Monroe”; these are anomalous districts with very low suicide risk. The academic factor, in contrast, is identified to have only common effects after scaling by the variances according to Definition 2, which makes the estimated model even more parsimonious. That the effect of the academic factor is always positive indicates that suicide risk tends to be higher in those school districts with better academic performance; as discussed in Chen and Aseltine (2017), students in school districts of better academic performance could be under higher pressure, which in turn may induce more psychological distress. In general, our results agree well with previous studies, and we gain additional insight on the changing impact of the school district characteristics on the suicide risk.

We have also compared Mix-HP-AL to Mix-AL by performing a random-splitting procedure to evaluate their out-of-sample predictive performance. Each time the data are split to 80% training for model fitting and 20% testing for out-of-sample evaluation, and the procedure is repeated 500 times. The average predictive log-likelihood (with standard error in the parenthesis) is $-24.6 (2.32)$ and $-23.2 (2.16)$ for Mix-AL and Mix-HP-AL, respectively, indicating that the proposed method indeed performs better for this dataset.

The proposed method has also been applied to another application in sports analytics for understanding how the
salaries of baseball players are associated with their performance and contractual status. Due to space limit, the application is detailed in Web Appendix G.

7 | DISCUSSION

In this paper, we propose a mixture regression method to thoroughly explore the heterogeneity in a population of interest, which is increasingly encountered in the era of big data. Our approach goes beyond the conventional variable selection methods, by not only identifying the relevant predictors, but also distinguishing from them the true sources of heterogeneity. As such, the proposed approach can potentially lead to a much more parsimonious and interpretable model to facilitate scientific discovery.

There are a number of future research directions. It is pressing to extend the proposed method to handle non-Gaussian outcomes, such as binomial mixture and Poisson mixture. This extension can help us to improve the analysis for the suicide risk study, as the raw counts of the suicide-related hospital admissions may be better modeled by Poisson distribution. Another possible direction is to consider other forms of penalty functions. For example, when the predictors are highly correlated, it could be beneficial to use the elastic-net penalty (Zou and Hastie, 2005) to ensure stable coefficient estimation. Nonconvex penalties could also be considered to improve variable selection. A related task is to extend the theoretical analysis to high-dimensional settings where the number of variables may grow with or exceed the sample size. A potential by-product of the proposed approach is that it can lead to automatic reduction of the number of prespecified clusters when the effects of some clusters are estimated to be exactly the same; it is hopeful that this interesting feature can allow us to build a more general mixture learning framework where relevant variables, sources of heterogeneity and the number of clusters are simultaneously learned. It would also be interesting to consider heterogeneity pursuit in multivariate mixture regression, but it is not straightforward. The mixture components may have different covariance matrices that complicate the definition of the sources of heterogeneity, and the set of predictors with heterogeneous effects may differ across different responses.
In this work, we mainly focus on the framework of mixture regression to pursue the sources of heterogeneity at the “global” level. An interesting direction is to extend our work to utilize the frameworks of individualized modeling and sub-group analysis that mainly pursue the sources of heterogeneity at the “individual” level (Tang et al., 2020). To lessen the assumptions of mixture regression, several recent works formulate the problem as a penalized regression with a fusion-type penalty. Ma and Huang (2017) proposed a concave pairwise fusion approach to identify sub-groups with pairwise penalization on subject-specific intercepts. Austin et al. (2020) proposed a grouping fusion approach to identify unknown sub-groups and their corresponding regression models. Tang et al. (2020) proposed a method to simultaneously achieve individualized variable selection and sub-grouping. Comparing to the mixture model framework, an individualized penalized regression approach may not fully utilize the potential global mixture structure and fails to consider the potential heterogeneity in variances. Therefore, we will explore the idea of combining mixture model and individualized fusion, to simultaneously perform global and individualized heterogeneity pursuits.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this paper are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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**SUPPORTING INFORMATION**

Web Appendices and Figures referenced in Sections 3–6 and the final lists of SNP names in ADNI analysis are available at the *Biometrics* website on Wiley Online Library. R package to implement the proposed approach is provided along with instructions to run the analyses.

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