Privacy Preserving Integrative Regression Analysis of High-dimensional Heterogeneous Data

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Abstract

Meta-analyzing multiple studies, enabling more precise estimation and investigation of generalizability, is important for evidence based decision making. Integrative analysis of multiple heterogeneous studies is, however, highly challenging in the high dimensional setting. The challenge is even more pronounced when the individual level data cannot be shared across studies due to privacy concerns. Under ultra high dimensional sparse regression models, we propose in this paper a novel integrative estimation procedure by aggregating and debiasing local estimators (ADeLE), which allows us to base solely on the derived data to perform estimation with general loss functions. The ADeLE procedure accommodates between study heterogeneity in both the covariate distribution and model parameters, and attains consistent variable selection. Furthermore, the prediction and estimation errors incurred by aggregating derived data is negligible compared to the statistical minimax rate. In addition, the ADeLE estimator is shown to be asymptotically equivalent in prediction and estimation to the ideal estimator obtained by sharing all data. The finite-sample performance of the ADeLE procedure is studied via extensive simulations. We further illustrate the utility of the ADeLE procedure to derive phenotyping algorithms for coronary artery disease using electronic health records data from multiple disease cohorts.

Keywords: Debiased Lasso; Heterogeneity; Privacy Constraints; Prediction and Estimation Equivalence; Rate Optimality; Sparse Meta-analysis; Sparsistency.

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1. INTRODUCTION

Synthesizing information from multiple studies is crucial for evidence based medicine and policy making. Meta-analyzing multiple studies allows for more precise estimates and enables investigation of generalizability. In the presence of heterogeneity across studies and high dimensional predictors, such integrative analysis however is highly challenging. An example of such integrative analysis is to develop generalizable predictive models using electronic health records (EHR) data from different hospitals. In addition to high dimensional features, EHR data analysis encounters privacy constraints in that individual level data typically cannot be shared across hospitals, which makes the challenge of integrative analysis even more pronounced. Breach of Privacy arising from data sharing is in fact a growing concern in general for scientific studies (Erlich and Narayanan, 2014; Fecher et al., 2015).

Such privacy concern calls for integrative analysis approaches that rely only on summary statistics from the distributed local sites, without requiring any individual-level information to be shared across sites (Zöller et al., 2018). In the context of high dimensional regression modeling, there are several distributed learning and meta-analysis approaches that aim to address such concerns. For example, Battey et al. (2018), Lee et al. (2017) and Tang et al. (2016) proposed distributed inference procedures for high dimensional regression by integrating the local debiased LASSO estimators (Zhang and Zhang, 2014; Van de Geer et al., 2014). Li et al. (2016) and Lu et al. (2015) proposed privacy-preserving approaches for $L_2$-regularized logistic and Cox regression, which rely on iterative communications across the studies. Such methods require sequential communications between local sites and the central machine, which may be time and resource consuming, especially since human effort is often needed to perform the computation. More recently, with no communication with the individual-level data across the local sites, Jordan et al. (2018) presented a communication-efficient surrogate likelihood framework for distributed statistical inference.
However, the aforementioned distributed learning approaches all assume the model homogeneity among the local sites. To incorporate the model heterogeneity, under a low dimensional setting where the covariate dimension $p$ is small relative to the sample size $n$, He et al. (2016) proposed a sparse meta-analysis approach (SMA) to integrate information across sites. Nevertheless, the SMA method relies on the maximum likelihood estimator (MLE) in each local site and hence is not applicable when $p$ is large relative to $n$. Under a high dimensional setting, there is a paucity of privacy preserving methods that can perform integrative analysis in the presence of heterogeneity. To fill this gap, we propose in this paper a novel integrative estimation procedure by aggregating and debiasing local estimators (ADeLE). The ADeLE approach aggregates privacy preserving summary statistics from the local cites while accommodating heterogeneity in model parameters across sites.

Compared to existing distributed high dimensional inference procedures (Battey et al., 2018; Lee et al., 2017; Lu et al., 2015, e.g), the ADeLE approach requires less assumptions on the structure of the design matrix and is more computationally efficient in that no debiasing is needed when deriving site-specific summary statistics. We refer the details to Section 3. In addition, under ultra-high dimensional regime where $p$ can grow exponentially with $n$, our estimator is shown to theoretically achieve asymptotically equivalent performance with the estimator obtained by the ideal individual patient data (IPD) pooled across sites and attain consistent variable selection under some sparsity assumptions. Such properties are not readily available in the existing literature. Numerical results suggest that the proposed method outperforms existing methods and enjoys similar performance as the ideal IPD estimator. The ADeLE approach solves LASSO problem only once in each local site without requiring the computation of the inverse Hessian matrices or the debiased estimators and only needs one turn in communication, and is thus efficient both in computation and communication.

The rest of this paper is organized as follows. We introduce the setting in Section 2
and describe the ADeLE approach in Section 3. Theoretical properties of the ADeLE are studied in Section 4. We derive the upper bound for the prediction and estimation risks of the ADeLE, and show that the errors incurred by aggregating derived data is negligible compared to the statistical minimax rate. When the true model is ultra-sparse, the ADeLE is shown to be asymptotically equivalent to the IPD estimator and achieves sparsistency. Section 5 compares the performance of the ADeLE approach to existing methods through simulations. We apply the ADeLE approach to derive classification models for coronary artery disease (CAD) using electronic health records (EHR) data from four different disease cohorts in Section 6. Section 7 concludes the paper with a discussion. Technical proofs of the theoretical results are provided in the Supplementary Materials.

2. SPARSE INTEGRATIVE ANALYSIS

Suppose there are $M$ independent studies and $n_m$ subjects in the $m$th study, for $m = 1, \ldots, M$. For the $i$th subject in the $m$th study, let $Y_i^{(m)}$ and $X_i^{(m)}$ respectively denote the response and the $p$-dimensional covariate vector, $D_i^{(m)} = (Y_i^{(m)}, X_i^{(m)})^T$, $Y^{(m)} = (Y_1^{(m)}, \ldots, Y_{n_m}^{(m)})^T$, and $X^{(m)} = (X_1^{(m)}, X_2^{(m)}, \ldots, X_{n_m}^{(m)})^T$. We assume that the observations in study $m$, $\mathcal{D}^{(m)} = \{D_i^{(m)}, i = 1, \ldots, n_m\}$, are independent and identically distributed. Without loss of generality, we assume that $X_i^{(m)}$ includes 1 as the first component and $X_{i,-1}^{(m)}$ has mean $\mathbf{0}$ with covariance matrix $\Sigma_{0,-1}^{(m)} = \text{Cov}(X_{i,-1}^{(m)})$, where for any vector $\mathbf{x} = (x_1, x_2, \ldots, x_d)^T \in \mathbb{R}^d$, $\mathbf{x}_{-1} = (x_2, \ldots, x_d)^T$. Let $X = \text{diag}\{X^{(1)}, \ldots, X^{(M)}\}$. We define the population parameters of interest as

$$
\beta_0^{(m)} = \arg\min_{\beta^{(m)}} \mathcal{L}_m(\beta^{(m)}), \quad \text{where } \mathcal{L}_m(\beta^{(m)}) = \mathbb{E}\{f(\beta^{(m)}^T X_i^{(m)}, Y_i^{(m)})\}, \quad \beta^{(m)} = (\beta_1^{(m)}, \beta_2^{(m)}, \ldots, \beta_p^{(m)})^T
$$

for some specified loss function $f$. We assume that $\beta^{(m)}$ varies across studies but may share similar support and magnitude, which makes it possible to gain more accurate estimation
by combining the regression models across the studies. We will define such structure more rigorously in Section 2.1. Examples of loss function include \( f(\beta^T x, y) = (y - \beta^T x)^2 \) for linear regression and \( f(\beta^T x, y) = -y\beta^T x + \log\{1 + \exp(\beta^T x)\} \) for logistic regression.

Throughout, for any integer \( d, [d] = \{1, \ldots, d\} \). For any vector \( x = (x_1, x_2, \ldots, x_d)^T \in \mathbb{R}^d \), any matrix \( A = [A_1, \ldots, A_d] \in \mathbb{R}^{n \times d} \) and index set \( S = \{j_1, \ldots, j_k : j_1 < \cdots < j_k\} \subseteq [d] \), \( x_S = (x_{j_1}, \ldots, x_{j_k})^T \), \( \|x\|_q \) denotes the \( \ell_q \) norm of \( x \), \( \|x\|_\infty = \max_{j \in [d]} |x_j| \), \( \|x\|_2 = \|x\|_2/n^{1/2} \), \( A_{j,:} \) and \( A_{:j} \) respectively denote the \( j^{th} \) row and column of \( A \), \( A_{S,:} = [A_{j_1,:}, \ldots, A_{j_k,:}] \), \( \|A\|_2 := [\Lambda_{\max}(A^T A)]^{1/2} \), \( \|A\|_\infty = \max_j \|A_{j,:}\|_1 \). We let \( \beta_j = (\beta_j^{(1)}, \ldots, \beta_j^{(M)})^T \), \( \beta^{(*)} = (\beta^{(1)}T, \ldots, \beta^{(M)}T)^T \), and let \( \beta_{0,j} \) and \( \beta^{(*)}_{0} \) respectively denote the true values of \( \beta_j \) and \( \beta^{(*)} \).

2.1 Integrative Analysis of \( M \) Studies

To estimate \( \beta^{(*)} \) based on \( D^{(*)} = \{D^{(1)}, \ldots, D^{(M)}\} \), consider the empirical global loss function

\[
\tilde{L}(\beta^{(*)}) = N^{-1} \sum_{m=1}^M n_m \tilde{L}_m(\beta^{(m)}),
\]

where \( N = \sum_{m=1}^M n_m \) and

\[
\tilde{L}_m(\beta^{(m)}) = n_m^{-1} \sum_{i=1}^{n_m} f(\beta^{(m)}T X_i^{(m)}, Y_i^{(m)}), \quad m = 1, \ldots, M.
\]

Minimizing \( \tilde{L}(\beta^{(*)}) \) is obviously equivalent to estimating \( \beta^{(m)} \) using \( D^{(m)} \) only. To improve the estimation of \( \beta^{(*)}_0 \) by synthesizing information from \( D^{(*)} \) and overcome the high dimensionality, we assume that \( \beta^{(*)}_0 \) is sparse and employ penalized loss functions, \( \tilde{L}(\beta^{(*)}) + \lambda \rho(\beta^{(*)}) \), with the penalty function \( \rho(\cdot) \) designed to leverage prior information on \( \beta^{(*)}_0 \).

Under a prior assumption that \( \beta_{0,-1}^{(1)}, \ldots, \beta_{0,-1}^{(M)} \) share the same support, we may choose \( \rho(\cdot) \) as the group LASSO penalty (Yuan and Lin, 2006) \( \rho_1(\beta) = \sum_{j=2}^p \|\beta_j\|_2 \). If \( \beta_{0,-1}^{(1)}, \ldots, \beta_{0,-1}^{(M)} \) share similar support and magnitude, we decompose \( \beta_j^{(m)} \) as \( \beta_j^{(m)} = \mu_j + \alpha_j^{(m)} \) and impose a
mixture of LASSO and group LASSO penalty similarly as Cheng et al. (2015):

\[ \rho_2(\beta^{\bullet}) = \sum_{j=2}^{p} |\mu_j| + \lambda_g \sum_{j=2}^{p} \|\alpha_j\|_2, \]  

(1)

where \( \alpha_j = (\alpha_j^{(1)}, \ldots, \alpha_j^{(M)})^T \), \( 1_{M \times 1} \alpha_j = 0 \) for identifiability and \( \lambda_g \geq 0 \) is a tuning parameter. The center \( \mu_j \) represents average effect of the covariate \( X_j \) and \( \alpha_j \) captures the between study heterogeneity of the effects. We shall note here that \( \rho_2 \) in (1) slightly differs from Cheng et al. (2015) in that they penalize between study heterogeneity using \( \|\alpha_j,-1\|_2 \) while we use \( \|\alpha_j\|_2 \) instead. The modified penalty function has two main advantages: (1) it is invariant to the permutation of the indices of the \( M \) studies; and (2) it yields better theoretical estimation error bounds as will be studied in full detail in Section 4. This penalty accommodates three type of covariates: (i) homogeneous effect with \( \mu_j \neq 0 \) and \( \alpha_j = 0 \); (ii) heterogeneous effect with \( \alpha_j \neq 0 \); (iii) null effect with \( \mu_j = 0 \) and \( \alpha_j = 0 \).

With a given penalty function \( \rho(\cdot) \), we may form a penalized loss \( \hat{Q}(\beta^{\bullet}) = \hat{L}(\beta^{\bullet}) + \lambda_r \rho(\beta^{\bullet}) \) and an idealized IPD estimator for \( \beta_0^{\bullet} \) can be obtained as

\[ \hat{\beta}^{\bullet} = \arg\min_{\beta^{\bullet}} \hat{Q}(\beta^{\bullet}), \]  

which we refer to as the IPD estimator hereafter, with some tuning parameter \( \lambda_r \geq 0 \).

2.2 Sparse Meta-analysis (SMA) Approach

The IPD estimator \( \hat{\beta}^{\bullet} \) given in (2) is not feasible under privacy constraints as it requires sharing of the individual data across studies. Our goal is to construct an alternative estimator that asymptotically attains the same efficiency as \( \hat{\beta}^{\bullet} \) but only require sharing privacy preserving derived data. When \( p \) is not large, the SMA approach by He et al. (2016) achieves this goal via a second order Taylor expansion and estimates \( \beta^{\bullet} \) as \( \hat{\beta}^{\bullet}_{SMA} = \arg\min_{\beta^{\bullet}} \hat{Q}_{SMA}(\beta^{\bullet}) \),
where

$$\hat{Q}_{\text{SMA}}(\beta^\star) = N^{-1} \sum_{m=1}^{M} (\beta^{(m)} - \tilde{\beta}^{(m)})^\top \tilde{\nabla}^{-1}_{m} (\beta^{(m)} - \tilde{\beta}^{(m)}) + \lambda \rho(\beta^\star),$$

(3)

$\rho(\beta^\star)$ is the hierarchical LASSO penalty \cite{zhou2010}, $\tilde{\beta}^{(m)} = \text{argmin}_{\beta^{(m)}} \hat{L}_{m}(\beta^{(m)})$ and $\tilde{\nabla}_{m} = \{n_{m}^{-1}\nabla^{2} \hat{L}_{m}(\tilde{\beta}^{(m)})\}^{-1}$. When $\beta^{(m)}$ is the same across sites and $\lambda = 0$, $\hat{\beta}_{\text{SMA}}$ is the inverse variance weighted estimator \cite{lin2010}. Although the SMA attains oracle property for a relatively small $p$, it fails when $p$ is large due to the failure of $\tilde{\beta}^{(m)}$.

3. AGGREGATING AND DEBIASING LOCAL ESTIMATOR (ADELE)

3.1 ADeLE Method

In the high dimensional setting, one may overcome the limitation of the SMA approach by replacing $\tilde{\beta}^{(m)}$ with the regularized LASSO estimator,

$$\hat{\beta}^{(m)}_{\text{LASSO}} = \text{argmin}_{\beta^{(m)}} \hat{L}_{m}(\beta^{(m)}) + \lambda_{m} \|\beta^{(m)} - 1\|_{1},$$

(4)

However, aggregating $\{\hat{\beta}^{(m)}_{\text{LASSO}}, m \in [M]\}$ is problematic with large $p$ due to their inherent biases. To overcome the bias issue, we build the ADeLE method upon the debiasing approach for LASSO \cite{van2014} yet achieve debiasing without having to perform debiasing for $M$ local estimators.

Recall that the debiased LASSO estimator for $\beta^{(m)}_{0}$ is

$$\hat{\beta}^{(m)}_{\text{allasso}} = \hat{\beta}^{(m)}_{\text{LASSO}} - \hat{\Theta}^{(m)} \nabla \hat{L}_{m}(\hat{\beta}^{(m)}_{\text{LASSO}}), \quad \text{for } m = 1, \ldots, M,$$

(5)

where $\hat{\Theta}^{(m)}$ is a regularized inverse of the hessian matrix $\hat{H}_{m} \equiv -\nabla^{2} \hat{L}_{m}(\hat{\beta}^{(m)}_{\text{LASSO}})$. Instead of relying on (5) which requires performing debiasing $M$ times, we propose the ADeLE
estimator for $\beta_0^\ast$ as $\tilde{\beta}_{ADeLE} = \text{argmin}_{\beta^\ast} \hat{Q}_{ADeLE}(\beta^\ast)$, where

$$
\hat{Q}_{ADeLE}(\beta^\ast) = N^{-1} \sum_{m=1}^{M} n_m \left\{ \beta^{(m)^T} \tilde{H}_m \beta^{(m)} - 2\beta^{(m)^T} \tilde{g}_m \right\} + \lambda \rho(\beta^\ast).
$$

(6)

and $\tilde{g}_m = \tilde{H}_m \tilde{\beta}_{LASSO}^{(m)} - \nabla \hat{L}_m (\tilde{\beta}_{LASSO}^{(m)})$. The construction of $\hat{Q}_{ADeLE}(\beta^\ast)$ is motivated by

$$
N^{-1} \sum_{m=1}^{M} n_m (\beta^{(m)} - \tilde{\beta}_{LASSO}^{(m)})^T \tilde{H}_m (\beta^{(m)} - \tilde{\beta}_{LASSO}^{(m)}) + \lambda \rho(\beta^\ast)
$$

$$
= N^{-1} \sum_{m=1}^{M} n_m \left[ \beta^{(m)^T} \tilde{H}_m \beta^{(m)} - 2\beta^{(m)^T} \tilde{H}_m \tilde{\beta}_{LASSO}^{(m)} \right] + \lambda \rho(\beta^\ast) + C(\tilde{\beta}_{LASSO}^{(m)}; \tilde{\theta})
$$

$$
\approx N^{-1} \sum_{m=1}^{M} n_m \left\{ \beta^{(m)^T} \tilde{H}_m \beta^{(m)} - 2\beta^{(m)^T} \tilde{g}_m \right\} + \lambda \rho(\beta^\ast) + C(\tilde{\beta}_{LASSO}^{(m)}; \tilde{\theta}).
$$

where we used $\tilde{\theta}^{(m)} \approx \tilde{H}_m \approx I$, the identity matrix, in the above approximation. The ADeLE approach is privacy preserving as $\hat{Q}_{ADeLE}(\beta^\ast)$ depends on $\mathcal{D}^{(m)}$ only through $\hat{D}_m = \{n_m, \tilde{H}_m, \tilde{g}_m\}$. The ADeLE procedure is also computationally and statistically efficient as it achieves debiasing without calculating $\tilde{\theta}^{(m)}$, which can only be estimated well under strong conditions [Van de Geer et al., 2014].

When $\rho$ is either the group LASSO or the mixture penalty, the ADeLE can be implemented using coordinate descent algorithms [Friedman et al., 2010]. For the mixture penalty, we may carry out the algorithm via reparameterization. To this end, let $\mu = (\mu_1, \ldots, \mu_p)^T$, $\mathcal{X}^\ast = (\mathcal{X}_1^{(T)}, \ldots, \mathcal{X}_p^{(T)})^T$ and $\mathcal{X}^\ast_{-1} = (\mathcal{X}_{-1}^{(T)}, \ldots, \mathcal{X}_{-1}^{(T)})^T$. Also let $\mu_0$ and $\mathcal{X}_0$ be the true value of $\mu$ and $\mathcal{X}$. Define that $||\mathcal{X}^\ast_{-1}||_{2,1} = \sum_{j=2}^{p} ||\mathcal{X}_j||_2$. Let $\hat{Q}_{ADeLE}(\mu, \mathcal{X}^\ast) = \hat{L}_{ADeLE}(\mu, \mathcal{X}^\ast) + \lambda \rho_2(\mu, \mathcal{X}^\ast; \lambda_g)$, where $\rho_2(\mu, \mathcal{X}^\ast; \lambda_g) = ||\mu_{-1}||_1 + \lambda_g ||\mathcal{X}^\ast_{-1}||_{2,1}$ and

$$
\hat{L}_{ADeLE}(\mu, \mathcal{X}^\ast) = N^{-1} \sum_{m=1}^{M} n_m \left\{ (\mu^T + \mathcal{X}^{(m)^T}) \tilde{H}_m (\mu + \mathcal{X}^{(m)}) - 2\tilde{g}_m^T (\mu + \mathcal{X}^{(m)}) \right\}.
$$
Then the optimization problem in (6) can be reparameterized and represented as:

$$(\hat{\mu}_{ADeLE}, \hat{\alpha}_{ADeLE}^{(\bullet)}) = \arg\min_{(\mu, \alpha^{(\bullet)})} \hat{Q}_{ADeLE}(\mu, \alpha^{(\bullet)}), \quad \text{s.t. } \mathbf{1}_{M \times 1}^T \alpha_j = 0, \ j \in [p],$$

and $\hat{\beta}_{ADeLE}$ is obtained with the transformation: $\beta_j^{(m)} = \mu_j + \alpha_j^{(m)}$ for every $j \in [p]$.

### 3.2 Tuning Parameter Selection

The implementation of ADeLE requires selection of three sets of tuning parameters, $\{\lambda_m, m \in [M]\}$, $\lambda$ and also $\lambda_g$ if $\rho = \rho_2$. We select $\{\lambda_m, m \in [M]\}$ for the LASSO problem via the standard K-fold cross validation (CV). For conciseness of presentation, we focus on the tuning of $\lambda$ and $\lambda_g$ for the case with $\rho = \rho_2$ and note that similar strategies can be employed for tuning $\lambda$ when $\rho = \rho_1$. Selecting $\lambda$ and $\lambda_g$ needs to balance the trade-off between the model’s degrees of freedom, denoted by $\text{DF}(\lambda, \lambda_g)$, and the quadratic loss in $\hat{Q}_{ADeLE}(\beta^{(\bullet)})$. It is not feasible to tune $\lambda$ and $\lambda_g$ via the CV since individual-level data are not available in the central machine. We propose to select $\lambda$ and $\lambda_g$ as the minimizer of the generalized information criterion (GIC) [Wang and Leng, 2007, Zhang et al., 2010], defined as

$$\text{GIC}(\lambda, \lambda_g) = \text{Deviance}(\lambda, \lambda_g) + \gamma_N \text{DF}(\lambda, \lambda_g),$$

where $\gamma_N$ is some pre-specified scaling parameter and

$$\text{Deviance}(\lambda, \lambda_g) = N^{-1} \sum_{m=1}^M n_m \left\{ \hat{\beta}_{ADeLE}^{(m)^T}(\lambda, \lambda_g) \hat{\beta}_{ADeLE}^{(m)}(\lambda, \lambda_g) - 2 \hat{g}_m^T \hat{\beta}_{ADeLE}^{(m)}(\lambda, \lambda_g) \right\}. $$

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Let $\hat{S}_\mu = \{ j : \hat{\mu}_{\text{ADELE}, j}(\lambda, \lambda_g) \neq 0 \}$, $\hat{S}_\alpha = \{ j : \| \hat{\alpha}_{\text{ADELE}, j}(\lambda, \lambda_g) \|_2 \neq 0 \}$. Following Zhang et al. (2010) and Vaiter et al. (2012), we define $DF(\lambda, \lambda_g)$ as the trace of

$$
\left[ \partial^2_{\hat{S}_\mu, \hat{S}_\alpha} \hat{Q}_{\text{ADELE}}(\hat{\mu}_{\text{ADELE}}, \hat{\alpha}_{\text{ADELE}}) \right]^{-1} \left[ \partial^2_{\hat{S}_\mu, \hat{S}_\alpha} \hat{L}_{\text{ADELE}}(\hat{\mu}_{\text{ADELE}}, \hat{\alpha}_{\text{ADELE}}) \right],
$$

with the operator $\partial^2_{\hat{S}_\mu, \hat{S}_\alpha}$ defined as the second order partial derivative with respect to $(\mu^{(1)}_{\hat{S}_\mu}, \alpha^{(1)}_{\hat{S}_\alpha}, \ldots, \alpha^{(m-1)}_{\hat{S}_\alpha}, \alpha^{(m+1)}_{\hat{S}_\alpha}, \ldots, \alpha^{(M)}_{\hat{S}_\alpha})^T$, after reparameterizing by plugging $\alpha^{(m)} = -(\alpha^{(1)} + \cdots + \alpha^{(m-1)} + \alpha^{(m+1)} + \cdots + \alpha^{(M)})$ into $\hat{Q}_{\text{ADELE}}(\mu, \alpha^{(*)})$ or $\hat{L}_{\text{ADELE}}(\mu, \alpha^{(*)})$. Note that the definition of $DF(\lambda, \lambda_g)$ is invariant to the choice of $m$.

As discussed in Kim et al. (2012), $\gamma_N$ can be chosen depending on the goal with commonly used examples including $\gamma_N = 2/N$ for AIC (Akaike, 1974), $\gamma_N = \log N/N$ for BIC (Bhat and Kumar, 2010), $\gamma_N = \log \log p \log N/N$ for modified BIC (Wang et al., 2009) and $\gamma_N = 2 \log p/N$ for RIC (Foster and George, 1994). For numerical studies in Sections 5 and 6 we used the BIC with $\gamma_N = \log N/N$.

**Remark 1.** It has been shown that the proper choice of $\gamma_N$ guarantees GIC’s model selection consistency under various divergence rates of the dimension $p$ (Kim et al., 2012). For example, for fixed $p$, GIC is consistent if $N \gamma_N \to \infty$ and $\gamma_N \to 0$. When $p$ diverges in polynomial rate $N^\xi$, then GIC is consistent provided that $\gamma_N = \log N/N$ (BIC) if $0 < \xi < 1/2$; $\gamma_N = \log \log p \log N/N$ (modified BIC) if $0 < \xi < 1$. When $p$ diverges in exponential rate $O(\exp(\kappa N^\xi))$ with $0 < \nu < \xi$, GIC is consistent as $\gamma_N = N^{\nu-1}$.

## 4. THEORETICAL RESULTS

In this section, we present theoretical properties of $\hat{\beta}_{\text{ADELE}}^{(*)}$. We only present results for $\rho(\beta^{(*)}) = \rho_2(\beta^{(*)})$ but note that our theoretical results can be extended to other sparse structures. In Sections 4.2 and 4.3 we derive theoretical consistency and equivalence for
the prediction and estimation risks of the ADeLE, under high dimensional sparse model and smooth loss function $f$. In addition, Section 4.4 shows that the ADeLE achieves sparsistency, i.e., variable selection consistency, for the non-zero sets of $\mu_0$ and $\alpha_0^{(*)}$. We begin with some notation and definitions that will be used throughout the paper.

4.1 Notation and Definitions

Following Javanmard and Montanari (2014), we define the sub-Gaussian norm of a random variable $X$ as $\|X\|_{\psi_2} := \sup_{q \geq 1} q^{-1/2} (E|X|^q)^{1/q}$ and define the sub-Gaussian norm of a random vector $X$ as $\|X\|_{\psi_2} := \sup_{x \in \mathbb{S}^{d-1}} \|x^T X\|_{\psi_2}$, where $\mathbb{S}^{d-1}$ is the unit sphere in $\mathbb{R}^d$. For any symmetric matrix $X$, let $\Lambda_{\min}(X)$ and $\Lambda_{\max}(X)$ denote its minimum and maximum eigenvalue respectively. Denote by $S_\mu = \{j : \mu_{0j} \neq 0\}$, $S_\alpha = \{j : \|\alpha_{0j}\|_2 \neq 0\}$ and $S_0 = S_\mu \cup S_\alpha$. Let $s_\mu = |S_\mu|$, $s_\alpha = |S_\alpha|$ and $s_0 = |S_0|$. We define the model complexity adjusted effective sample size for each study as $n_m^e = n_m / (s_0 \log p)$ and $n_{eff} = N / [s_0(M + \log p)]$, which are the main drivers for the rates of the proposed estimators. We also define the $L_1$ ball around $\beta_0^{(m)}$ as $B_r(\beta_0^{(m)}) = \{\beta \in \mathbb{R}^m : \|\beta - \beta_0^{(m)}\|_1 \leq r\}$. Let $f_1^{(1)}(a,y) = \partial f(a,y)/\partial a$, $f_1^{(1)}(a,y) = \partial^2 f(a,y)/\partial a^2$, and $\Omega_{\beta_0}(\beta_0^{(m)})_{n_m \times n_m} = \text{diag}\{f_1^{(1)}(\beta_0^{(m)^T} X_1^{(m)}, Y_1^{(m)}), \ldots, f_1^{(1)}(\beta_0^{(m)^T} X_{n_m}^{(m)}, Y_{n_m}^{(m)})\}$. For any $S_1, S_2 \subseteq [p]$, let

\[
\mathcal{Z}_{S_1,S_2}^{(-m)} = \begin{pmatrix}
X_{S_1}^{(m)} & -X_{S_2}^{(m)} & \cdots & -X_{S_1}^{(m)} & -X_{S_2}^{(m)} & \cdots & -X_{S_1}^{(m)} \\
X_{S_1}^{(1)} & X_{S_2}^{(1)} & \cdots & 0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\
X_{S_1}^{(m-1)} & 0 & \cdots & X_{S_2}^{(m-1)} & 0 & \cdots & 0 \\
X_{S_1}^{(m+1)} & 0 & \cdots & 0 & X_{S_2}^{(m+1)} & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots & \vdots & \ddots & \vdots \\
X_{S_1}^{(M)} & 0 & \cdots & 0 & 0 & \cdots & X_{S_2}^{(M)} \\
\end{pmatrix}
\]

and that

\[
\mathcal{W}_{S_1,S_2}^{(-m)}(\beta^{(*)}) = \text{diag}\{\Omega_{m_0}^{1}(\beta^{(m)}), \Omega_{1}^{2}(\beta^{(1)}), \ldots, \Omega_{m-1}^{2}(\beta^{(m-1)}), \Omega_{m+1}^{2}(\beta^{(m+1)}), \ldots, \Omega_{M}^{2}(\beta^{(M)})\}\mathcal{Z}_{S_1,S_2}^{(-m)}.
\]
For simplicity, we denote by $W^{(-m)}_{S_{ad}}(\beta^{(*)}) = W^{(-m)}_{S_{ad}}(\beta^{(*)})$ and $W^{(-m)}(\beta^{(*)}) = W^{(-m)}_{[p],[p]}(\beta^{(*)})$. Then $W^{(-m)}(\hat{\beta}_{LASSO})$ is the weighted design for $(\mu^T, \alpha^{(1)^T}, \ldots, \alpha^{(m-1)^T}, \alpha^{(m+1)^T}, \ldots, \alpha^{(M)^T})^T$ in the loss function $\tilde{L}_{ADeLE}(\mu, \alpha^{(*)})$, by plugging $\alpha^{(m)} = -(\alpha^{(1)} + \cdots + \alpha^{(m-1)} + \alpha^{(m+1)} + \cdots + \alpha^{(M)})$ into $\tilde{L}_{ADeLE}(\mu, \alpha^{(*)})$. In addition, we let $T = (I_{(M-1)\times 1}, I_{(M-1)\times (M-1)})^T$ be an $M \times (M-1)$ transformation matrix, and define $\|x\|_T := \|Tx\|_2$ for a vector $x \in \mathbb{R}^{M-1}$. In addition, for any matrix $A$, let $A^{\otimes 2} = A^T A$ and if $A$ is $(M-1) \times L$, define the conjugate norm of $\| \cdot \|_T$ as $\|A\|_T := \|T(T^{\otimes 2})^{-1} A\|_2$.

4.2 Prediction and Estimation Consistency

To establish theoretical properties of the local estimators and the ADeLE in terms of estimation and prediction risks, we first introduce some sufficient conditions.

**Condition 1.** There exists constants $C_{\min}$ and $C_{\max}$ that for any $m \in [M]$, $0 < C_{\min} \leq \Lambda_{\min}(\Sigma^{(m)}_{0,-1}) \leq \Lambda_{\max}(\Sigma^{(m)}_{0,-1}) \leq C_{\max} < \infty$.

**Condition 2.** For all $m \in [M]$ and $i \in [n_m]$, $X_{i,-1}^{(m)}(\Sigma^{(m)}_{0,-1})^{-1/2}$ is sub-Gaussian, i.e., there exists some constant $\kappa > 0$ that $\|X_{i,-1}^{(m)}(\Sigma^{(m)}_{0,-1})^{-1/2}\|_{\psi_2} < \kappa$.

**Condition 3.** The loss function $f(a, y)$ is convex in $a$ for any $y \in \mathcal{Y}$, where $\mathcal{Y} \subset \mathbb{R}$ denotes the support for $Y$. For all $m \in [M]$ and $i \in [n_m]$, $f'_i(\beta^{(m)^T}_0 X_i^{(m)} , Y_i^{(m)})$ is sub-Gaussian, conditional on $X_i^{(m)}$.

**Condition 4.** There exists positive constants $r$, $K_1$ and $K_2$ such that for all $D_i^{(m)}$ and $\beta^{(m)} \in \mathcal{B}_r(\beta^{(m)}_0)$: (i) $f''_1(X_i^{(m)^T} \beta^{(m)}, Y_i^{(m)}) = O(1)$ and is bounded away from 0; (ii) $|f''_1(\beta^{(m)^T}_0 X_i^{(m)}, Y_i^{(m)}) - f''_1(\beta^{(m)^T}_0 X_i^{(m)}, Y_i^{(m)})| \leq K_1 \|\beta^{(m)} - \beta^{(m)}_0\| X_i^{(m)}$, and (iii) $\max_i \|X_i^{(m)}\|_\infty \leq K_2$.

**Remark 2.** Conditions 1 and 2 are commonly assumed in the literature for deriving prediction and estimation consistency of LASSO estimators (Bühlmann and Van De Geer, 2011; Negahban et al., 2012). They regularize the data generating process and the tail behavior of
the design matrix $X$. Condition 3 controls the tail behavior of $f'_1(a, y)$ such that the random error $\nabla \hat{L}_m(\beta_0^{(m)})$ can be bounded properly. It is not difficult to verify that Condition 3 is satisfied by an extensive class of loss functions, for example, the logistics model. By Proposition 3.2 of (Rivasplata, 2012), such sub-Gaussian assumption in Conditions 2 and 3 is equivalent to the commonly used sub-Gaussian tail condition: $X$ is sub-Gaussian if there exists some constant $c > 0$ that for any $\lambda > 0$, $P(|X| \geq \lambda) \leq 2e^{-c\lambda^2}$. Condition 4 was assumed in (Van de Geer et al., 2014) to guarantee that the empirical Hessian matrix $\nabla^2 \hat{L}_m(\hat{\beta}_LASSO)$ is close enough to $\nabla^2 \hat{L}_m(\beta_0^{(m)})$, and the gradient term $\hat{g}_m = n_m[\hat{H}_m \hat{\beta}_LASSO - \nabla \hat{L}_m(\hat{\beta}_LASSO)]$ is close enough to $n_m[\nabla^2 \hat{L}_m(\beta_0^{(m)})\beta_0^{(m)} - \nabla \hat{L}_m(\beta_0^{(m)})]$. For Condition 4 (iii), $K_2$ is assumed to be a constant to simplify the technical details but it is not a necessary condition to attain the risk optimality. As an example, if $K_2$ grows in the order of $(\log p)^{1/2}$ for sub-Gaussian design $X^{(m)}$, we can simply modify the sparsity assumption accordingly to attain the optimality, as $K_2$ only appears in the excess term beyond the statistical minimax rate as shown in Theorem 4.

Lemma 1. (Risk bounds for Local Estimators) Under Conditions 1, 2, 4, there exists positive constants $C_0, c_1, C_{loc}$ and $\lambda_m \asymp (s_0n_m^{eff})^{-1/2}$ for each $m \in [M]$ that, when $n_m^{eff} \geq C_0$, with probability at least $1 - c_1 M/p$,

$$
\|\hat{\beta}_{LASSO}^{(m)} - \beta_0^{(m)}\|_1 \leq C_{loc} \sqrt{\frac{s_0}{n_m^{eff}}} \quad \text{and} \quad \|X^{(m)}(\hat{\beta}_{LASSO}^{(m)} - \beta_0^{(m)})\|_{(n_m)} \leq \frac{C_{loc}}{\sqrt{n_m^{eff}}}
$$

Lemma 1 shows that the local estimators meet the minimax optimal rates for high dimensional sparse model as provided in Raskutti et al. (2011).

Next, we present the risk bounds for the ADeLE including the prediction risk $\|X(\hat{\beta}_{ADELE}^{(*)} - \beta_0^{(*)})\|_{(N)}$ and estimation risks $\|\hat{\mu}_{ADELE} - \mu_0\|_1 + \lambda_9 \|\hat{\alpha}_{ADELE}^{(*)} - \alpha_0^{(*)}\|_{2,1}$ and $\|\hat{\beta}_{ADELE}^{(*)} - \beta_0^{(*)}\|_1$.

Theorem 1. (Risk bounds for the ADeLE) Assume all conditions of Lemma 1, $\hat{\beta}_{LASSO}^{(m)}$
\(B_r(\beta_0^{(m)}), \ n_m \approx N/M \) for all \( m \in [M] \), \( \lambda_g \approx M^{-\frac{1}{2}} \). Then there exists \( \lambda \approx (s_0n_{\text{eff}})^{-\frac{1}{2}} + K_1K_2(n_{\text{eff}}^{-1}) \), \( C_{AD} > 0 \) and \( c_1' > 0 \), such that, with probability at least \( 1 - c_1'M/p \),

\[
\|X(\hat{\beta}_{\text{ADE}}^{(m)} - \beta_0^{(m)})\|_{(N)} \leq C_{AD} \left( \frac{1}{\sqrt{n_{\text{eff}}}} + \frac{(s_0)^{\frac{1}{2}}K_1K_2}{n_{\text{eff}}^m} \right),
\]

\[
\|\hat{\mu}_{\text{ADE}} - \mu_0\|_1 + \lambda_g \|\hat{\alpha}_{\text{ADE}}^{(\bullet)} - \alpha_0^{(\bullet)}\|_{2,1} \leq C_{AD} \left( \sqrt{\frac{s_0}{n_{\text{eff}}} + \frac{s_0K_1K_2}{n_{\text{eff}}^m}} \right),
\]

and

\[
\|\hat{\beta}_{\text{ADE}}^{(\bullet)} - \beta_0^{(\bullet)}\|_1 \leq C_{AD} \left( M \sqrt{\frac{s_0}{n_{\text{eff}}} + \frac{s_0MK_1K_2}{n_{\text{eff}}^m}} \right).
\]

**Remark 3.** By Lemma 4, the condition \( \|\hat{\beta}_{\text{LASSO}}^{(m)} - \beta_0^{(m)}\|_1 < r \) in Theorem 1 holds when \( s_0 = o\{\sqrt{N/(M \log p)}\} \) or equivalently \( s_0 = o(n_{\text{eff}}^m) \), for large enough \( N \).

The second term in each of the upper bounds of Theorem 1 is the additional error incurred by combining derived data instead of raw data. These terms are asymptotically negligible under sparsity as \( s_0 = o(\sqrt{N(\log p + M)/(MK_1K_2 \log p)^2}) \) or equivalently \( s_0 = o\{n_{\text{eff}}^m/(\sqrt{n_{\text{eff}}K_1K_2})^2\} \). Thus \( \hat{\beta}_{\text{ADE}}^{(\bullet)} \) achieves the same error rate as the ideal estimator \( \hat{\beta}^{(\bullet)} \) obtained by combining raw data as shown in the following section, and is nearly rate optimal.

### 4.3 Asymptotic Equivalence in Prediction and Estimation

Under sparsity assumptions, we show in this section the asymptotic equivalence between \( \hat{\beta}_{\text{ADE}}^{(\bullet)} \) and the ideal estimator \( \hat{\beta}^{(\bullet)} \) with respect to the prediction and estimation risks.

**Theorem 2. (Asymptotic Equivalence)** Under all conditions of Theorem 1, when \( M = o(p) \) and \( s_0 = o\{n_{\text{eff}}^m/(\sqrt{n_{\text{eff}}K_1K_2})^2\} \), there exists \( \lambda_r \approx (s_0n_{\text{eff}})^{-\frac{1}{2}} \) such that, the IPD esti-
mator $\hat{\beta}^{(\bullet)}$ and $(\hat{\mu}^T, \hat{\alpha}^{(\bullet)T})^T$ with tuning parameter $\lambda_r$ in (2) satisfies
\[
\|X(\hat{\beta}^{(\bullet)} - \beta_0^{(\bullet)})\|_{(N)} = O_P \left( \frac{1}{\sqrt{n_{\text{eff}}}} \right) \quad \text{and} \quad \|\hat{\mu} - \mu_0\|_1 + \lambda_g \|\hat{\alpha}^{(\bullet)} - \alpha_0^{(\bullet)}\|_{2,1} = O_P \left( \sqrt{\frac{s_0}{n_{\text{eff}}}} \right).
\]
Furthermore, for some $\lambda_\Delta = o(\lambda_r)$, the above $\hat{\beta}^{(\bullet)}$ and the ADeLE defined by (6) with $\lambda = \lambda_r + \lambda_\Delta$ are equivalent in prediction and estimation in the sense that
\[
\|X(\hat{\beta}_{\text{ADeLE}}^{(\bullet)} - \beta_0^{(\bullet)})\|_{(N)} \leq \|X(\hat{\beta}^{(\bullet)} - \beta_0^{(\bullet)})\|_{(N)} + o_P \left( \frac{1}{\sqrt{n_{\text{eff}}}} \right);
\]
\[
\|\hat{\mu}_{\text{ADeLE}} - \mu_0\|_1 + \lambda_g \|\hat{\alpha}_{\text{ADeLE}}^{(\bullet)} - \alpha_0^{(\bullet)}\|_{2,1} \leq \|\hat{\mu} - \mu_0\|_1 + \lambda_g \|\hat{\alpha}^{(\bullet)} - \alpha_0^{(\bullet)}\|_{2,1} + o_P \left( \sqrt{\frac{s_0}{n_{\text{eff}}}} \right).
\]

Theorem 2 demonstrates the asymptotic equivalence between $\hat{\beta}_{\text{ADeLE}}^{(\bullet)}$ and $\hat{\beta}^{(\bullet)}$ with respect to estimation and prediction risks, and hence implies strict optimality of the ADeLE. Specifically, when $s_0 = o\{(n_{\text{eff}}/(\sqrt{n_{\text{eff}}}K_1K_2))^2\}$, the excess prediction and estimation risks of $\hat{\beta}_{\text{ADeLE}}^{(\bullet)}$ compared to $\hat{\beta}^{(\bullet)}$ are respectively no larger than $o_P(1/\sqrt{n_{\text{eff}}})$ and $o_P(\sqrt{s_0/n_{\text{eff}}})$ and smaller than the minimax optimal rates for multi-task learning of high dimensional sparse model (Lounici et al., 2011; Huang et al., 2010). To the best of our knowledge, such equivalence results have not been established yet for LASSO type estimators in existing distributed learning literature.

Remark 4. Existing work on high dimensional distributed $L_1$-regularized regression and inference (Jordan et al., 2018; Lee et al., 2017; Battey et al., 2018; Tang et al., 2016) assumes that $\beta^{(1)} = \beta^{(2)} = \cdots = \beta^{(M)} := \beta$ and employs the penalty $\rho(\beta) = \|\beta - 1\|_1$. Theorem 2 can be extended to this setting naturally. It leads to the conclusion that, under the same assumptions, let $\hat{\beta}_{\text{ADeLE}}, \hat{\beta}$ and $\beta_0$ be the ADeLE, the IPD estimator and the true value for the
coefficients $\beta$ respectively and denote by $\tilde{n}_{\text{eff}} = N/(s_0 \log p)$, when $s_0 = o\{\tilde{n}_{\text{eff}}(MK_1K_2)^{-2}\}$,

$$\|X(\hat{\beta}_{\text{ADeLE}} - \beta_0)\|_N \leq \|X(\hat{\beta} - \beta_0)\|_N + o_p\left(\frac{1}{\sqrt{\tilde{n}_{\text{eff}}}}\right),$$

and

$$\|\hat{\beta}_{\text{ADeLE}} - \beta_0\|_1 \leq \|\hat{\beta} - \beta_0\|_1 + o_p\left(\frac{s_0}{\tilde{n}_{\text{eff}}}\right).$$

Note that

$$\|X(\hat{\beta} - \beta_0)\|_N = O_p\left(\frac{1}{\sqrt{\tilde{n}_{\text{eff}}}}\right) \quad \text{and} \quad \|\hat{\beta} - \beta_0\|_1 = O_p\left(\frac{\sqrt{s_0}}{\tilde{n}_{\text{eff}}}\right).$$

Thus the IPD attains the optimal rate under this setting. This implies that $\hat{\beta}_{\text{ADeLE}}$ achieves rate optimality and is more efficient than the local LASSO estimation $\hat{\beta}_{\text{LASSO}}^{(m)}$ when $M$ diverges, by Lemma 7.

4.4 Sparsistency

In this section, we present theoretical results concerning the variable selection consistency of the ADeLE. We begin with some extra sufficient conditions for the sparsistency result.

**Condition 5.** There exists constants $r' > 0$ and $C'_{\min} > 0$ that for all $m \in [M]$ and $\beta^{(m)} \in \mathcal{B}_r(\beta_0^{(m)})$, $\Lambda_{\min}(X_{mS_0}^T \Omega_m(X^{(m)}S_0/N_m)) > C'_{\min}$.

**Condition 6.** There exists $\lambda_0 \asymp 1$, $\epsilon > 0$ and some constant $r' > 0$ that, for $\beta^{(\ast)} = (\beta^{(1)}^T, \ldots, \beta^{(M)}^T)^T$ satisfying $\beta^{(m)} \in \mathcal{B}_r(\beta_0^{(m)})$ for all $m$, we have that, for $j \in S_\mu^c$ and $j' \in S_\alpha^c$,

$$\min_{m \in [M]} \left\{ \left\| W_{j,0}^{(-m)}(\beta^{(\ast)})^T W_{S_{\text{full}}}^{(-m)}(\beta^{(\ast)}) \left[ W_{S_{\text{full}}}^{(-m)}(\beta^{(\ast)})^\otimes 2 \right]^{-1} \right\|_2 \right\} \leq \frac{1 - \epsilon}{\sqrt{\lambda_0^2Ms_\alpha + s_\mu}},$$

and

$$\min_{m \in [M]} \left\{ \left\| W_{j,j'}^{(-m)}(\beta^{(\ast)})^T W_{S_{\text{full}}}^{(-m)}(\beta^{(\ast)}) \left[ W_{S_{\text{full}}}^{(-m)}(\beta^{(\ast)})^\otimes 2 \right]^{-1} \right\|_T \right\} \leq \frac{\lambda_0^2 (1 - \epsilon)}{\sqrt{\lambda_0^2Ms_\alpha + s_\mu}}.$$
Condition 7. For any \( m \in [M], n_m \propto N/M \). Let \( \nu = \min\{\min_{j \in S_{\mu}} |\mu_{0j}|, \min_{j \in S_{\alpha}} \|\alpha_{0j}\|_\infty\} \).

For the \( \epsilon \) defined in Condition 6, \((\nu \epsilon)^{-1} M/\sqrt{n_m} \rightarrow 0, \) as \( N \rightarrow \infty \).

Remark 5. Conditions 5-7 are commonly used sparsistency assumptions for LASSO type estimators, and are similar to those of Nardi et al. (2008), for the sparsistency of group LASSO estimator in linear models. Condition 5 requires the eigenvalues for the covariance matrix of the weighted design matrix corresponding to \( S_0 \) to be bounded away from zero so that its inverse behaves well (Zhao and Yu, 2006). Condition 6 is the commonly used irrepresentable condition for the group LASSO (Nardi et al., 2008). Roughly speaking, it requires that the weighted design corresponding to \( S_{\text{full}} \) cannot be represented well by the weighted design for \( S_{c_{\text{full}}} \). Condition 7 means that the minimum magnitude of the coefficients must be large enough, to make the non-zero coefficients recognizable.

**Theorem 3. (Sparsistency)** Let \( \hat{S}_\mu = \{j : \hat{\mu}_{\text{ADE},j} \neq 0\} \) and \( \hat{S}_\alpha = \{j : \|\hat{\alpha}_{\text{ADE},j}\|_2 \neq 0\} \).

Denote the event \( \Theta_\mu = \{\hat{S}_\mu = S_\mu\} \) and \( \Theta_\alpha = \{\hat{S}_\alpha = S_\alpha\} \). Under Conditions 1-7 with \( M = o(p) \), \( s_0 = o\{n_m^{\alpha}(\sqrt{MK_1K_2})^{-2}\} \) and \( \lambda_g \asymp 1 \), and assume \( \lambda \) satisfies that

\[
\frac{\lambda \sqrt{s_0 M^3}}{\nu} + \frac{1}{\lambda \epsilon} \sqrt{\frac{\log p}{N}} \rightarrow 0,
\]

we have

\[
P(\Theta_\mu \cap \Theta_\alpha) \rightarrow 1 \quad \text{as} \quad N \rightarrow \infty.
\]

Remark 6. From Conditions 6 and 7, it is easy to see that \( \lambda \) defined in Theorem 3 exists, and is similar to the tuning parameter defined in Nardi et al. (2008). When \( M = O(\log p) \), the maximum rate of \( s_0 \) in Theorem 3 is the same as that in Theorem 2.

Remark 7. In Theorems 2 and 3, we allow \( M \), the number of studies, to diverge slowly
while still preserving theoretical properties. The growing rate of $M$ is allowed to be

$$M = \min \{ o(p), o(\sqrt{N/[s_0(K_1K_2)^2 \log p]}), o(N/[\sqrt{s_0K_1K_2 \log p}^2]) \}$$

for the equivalence result in Theorem 2 and

$$M = \min \{ o(p), o(\sqrt{N/[s_0(K_1K_2)^2 \log p]}), o(\sqrt{N\epsilon^2 \nu^2/[s_0 \log p]}) \}$$

for the sparsity result in Theorem 3.

5. SIMULATION STUDY

We present simulation results in this section to evaluate the performance of our proposed ADeLE estimator and to compare it with several other approaches. We let $M \in \{4, 8\}$ and $p \in \{40, 400, 3000\}$ and set $n_m = 800$ for each $m$. We let $\beta^{(m)} = \mu + \alpha^{(m)}$ and set

$$\left( \begin{array}{c} \mu^T \\ \alpha^{(2)T} \\ \alpha^{(3)T} \\ \alpha^{(4)T} \end{array} \right) = \left( \begin{array}{cccc} 0 & 0.25 \cdot 1_{1\times5} & 0.25 \cdot 1_{1\times5} & 0_{1\times5} & 0_{1\times(p-16)} \\ 0 & 0.25 \cdot 1_{1\times5} & 0_{1\times5} & 0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \\ 0 & -0.25 \cdot 1_{1\times5} & 0_{1\times5} & -0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \\ 0 & -0.25 \cdot 1_{1\times5} & 0_{1\times5} & -0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \end{array} \right),$$

when $M = 4$ and additionally introduce:

$$\left( \begin{array}{c} \alpha^{(5)T} \\ \alpha^{(6)T} \\ \alpha^{(7)T} \\ \alpha^{(8)T} \end{array} \right) = \left( \begin{array}{cccc} 0 & 0.25 \cdot 1_{1\times5} & 0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \\ 0 & 0.25 \cdot 1_{1\times5} & 0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \\ 0 & -0.25 \cdot 1_{1\times5} & -0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \\ 0 & -0.25 \cdot 1_{1\times5} & -0.25 \cdot 1_{1\times5} & 0_{1\times(p-16)} \end{array} \right).$$
when $M = 8$. Covariates $\mathbf{X}^{(m)}$ are generated from AR(1) model with marginal distribution $N(0,1)$ and auto-correlation coefficient 0.3. We generate the binary response $\mathbf{Y}^{(m)}$ from a logistics model of $\expit(\mathbf{X}^{(m)}\beta^{(m)})$ and use the logistic loss for estimation. For each setting, we summarize the results based on 200 simulated datasets.

We include four other methods for comparison: (i) the ideal IPD estimator $\hat{\beta}^{(•)} = \arg\min_{\beta^{(•)}} \hat{Q}(\beta^{(•)})$, (ii) the SMA estimator [He et al., 2016] when $p = 40$ and $p = 400$; (iii) the SMA after Sure Independent Screening (SIS-SMA) estimator when $p = 400$ and $p = 3000$ for which we first implement marginal screening as in Fan and Lv (2008) to reduce the dimension from $p$ to $N/(3 \log N)$, a threshold used by He et al. (2016), and then implement SMA on the union of the $M$ reduced sets of covariates; and (iv) the regularized quadratic regression (Quad) estimator defined as $\arg\min_{\beta^{(•)}} N^{-1} \sum_{m=1}^{M} \{ \beta^{(m)^T} \mathbf{X}^{(m)^T} \mathbf{X}^{(m)} \beta^{(m)} - 2\beta^{(m)^T} (\mathbf{X}^{(m)^T} \mathbf{Y}^{(m)}) \} + \lambda \rho(\beta^{(•)})$, which is also privacy preserving since it only requires sharing of $\mathbf{X}^{(m)^T} \mathbf{Y}^{(m)}$ and $\mathbf{X}^{(m)^T} \mathbf{X}^{(m)}$. We summarize the average absolute estimation error (AEE), $||\beta^{(•)} - \beta^{(•)}_0||_1$, and the prediction error (PE), $||\mathbf{X}(\beta^{(•)} - \beta^{(•)}_0)||_{(N)}$, for the estimators obtained from the aforementioned methods in Figure 1 for $M = 4$ and in Figure 2 for $M = 8$. For support recovery, we also present in Figures 1 and 2 the true positive rate (TPR) and false discovery rate (FDR) in identifying $\mathcal{S}_\mu$ for the homogeneous effects and $\mathcal{S}_\alpha$ for the heterogeneous effects.

Consistent with the theoretical equivalence results, the ADeLE estimator attained similar estimation and prediction accuracy as that of the idealized IPD estimator. The ADeLE estimator is substantially more accurate than that of the SMA or SMA-SIS when $p = 400$ and $p = 3000$ and is more efficient than the SMA even when $p = 40$. This could be attributed to the improved performance of the local LASSO estimator $\hat{\beta}_{\text{LASSO}}^{(m)}$ over the MLE $\bar{\beta}^{(m)}$ on sparse models. Although SMA-SIS performs better than the SMA when $p = 400$ by removing noisy variables, the PE and AEE of the ADeLE are 54% and 25% lower than
that of the SMA-SIS when $M = 4$ and 58% and 31% lower than that of the SMA-SIS when $M = 8$. The poor performance of SMA and SIS-SMA when $p = 400$ and 3000 can be in part attributed to the fact that the variance of MLE is excessively large as $p$ diverges and the marginal screening is not highly effective when the covariates are correlated. Our method also outperforms Quad in estimation accuracy across all settings. For example, the AEE estimates for $p = (40, 400, 3000)$ were $(15.4, 20.4, 23.3)$ for ADeLE and $(17.2, 21.0, 23.6)$ for Quad when $M = 8$. The difference of the two methods gets smaller when $p$ increases. This is mainly due to the fact that the errors from estimating $\theta$ contribute more in large $p$ and the two methods have similar performance in estimating $\theta$. For support recovery, ADeLE and IPD generally attain comparable TPR and FDR for both homogeneous and heterogeneous effects. The Quad procedure generally yields similar TPR but slightly higher FDR while the SIS-SMA and SMA perform poorly in support recovery. For identifying the support of $S_\mu$, the TPR and FDR for ADeLE and IPD are near identical to each other with near perfect TPR and FDR controlled around 20% or lower when $M = 4$ and around 10% when $M = 8$, even when $p = 3000$. For the support of $S_\alpha$, ADeLE and IPD generally have similar TPRs but the FDR is slightly higher for ADeLE particularly when $p = 3000$. For $p = (40, 400, 3000)$, ADeLE and IPD respectively attained TPR of $(1.00, 0.99, 0.90)$ and $(1.00, 0.99, 0.93)$ and FDR of $(0.09, 0.17, 0.16)$ and $(0.08, 0.14, 0.12)$ when $M = 8$. On the other hand, the slight increase in the inclusion of noisy variables has negligible impact on the estimation and prediction accuracy of $\hat{\beta}$.

6. APPLICATION TO EHR PHENOTYPING IN MULTIPLE DISEASE COHORTS

The development of next-generation cohort studies that link EHR data with biorepositories containing “-omics” information has expanded the opportunities for biomedical research [Kho et al., 2011]. With the growing availability of these high-dimensional data, the bottle-
neck in clinical research has shifted from a paucity of biologic data to a paucity of high-quality phenotypic data. Accurately and efficiently annotating patients with disease characteristics among millions of individuals is a critical step in fulfilling the promise of using EHR data for precision medicine. Novel machine learning based phenotyping methods leveraging a large number of predictive features have improved the accuracy and efficiency of existing phenotyping methods (Liao et al., 2015; Yu et al., 2015).

Existing phenotyping algorithms are often developed for a specific patient population although portability of phenotyping algorithms across multiple patient cohorts is of great interest. To investigate the portability issue and develop EHR phenotyping algorithms for coronary artery disease (CAD) useful for multiple cohorts, Liao et al. (2015) developed an CAD algorithm using a cohort of rheumatoid arthritis (RA) patients and applied the algorithm to other disease cohorts using EHR data from Partner’s Healthcare System. Here, we performed integrative analysis of multiple EHR disease cohorts to develop disease specific CAD algorithms for four diseases, including type 2 diabetes mellitus (DM), inflammatory bowel disease (IBD), multiple sclerosis (MS) and RA. Our proposed ADeLE algorithm enables us to let the data determine if a single algorithm can perform well across four disease cohorts or disease specific algorithms are needed.

For algorithm training, clinical investigators have manually curated gold standard labels on the CAD status, $Y$, for $N_1 = 172$ DM patients, $N_2 = 230$ IBD patients, $N_3 = 105$ MS patients and $N_4 = 760$ RA patients. There are a total of $p = 835$ candidate features including both codified features, narrative features extracted via natural language processing (NLP) (Zeng et al., 2006), as well as their two-way interactions. Examples of codified features include demographic information, lab results, medication prescriptions, counts of International Classification of Diseases (ICD) codes and Current Procedural Terminology (CPT) codes. Since patients may not have certain lab measurements and missingness is
highly informative, we also create missing indicators for the lab measurements as additional features. Examples of NLP terms include mentions of CAD, current smoking (CSMO), non smoking (NSMO) and CAD related procedures. Since the count variables such as the total number of CAD ICD codes are zero-inflated and skewed, we take \( \log(x + 1) \) transformation and include \( I(x = 0) \) as additional features for each count variable \( x \).

For each cohort, we randomly select 50% of the observations to form the training set for developing the CAD phenotyping algorithms and use the remaining 50% for validation. We used the logistic loss with the mixture penalty \( \rho_2 \). Other methods described in Section \( \text{S} \) including SIS-SMA and Quad are also applied for comparison. We only report results based on tuning parameters selected with BIC as in the simulation studies since the results obtained from AIC are largely similar in terms of prediction performance. Furthermore, to verify the improvement of the performance by combining the four datasets, we include the LASSO estimator for each local dataset (Local) as a comparison.

In Table 1, we present the estimated coefficients for variables that received non-zero coefficients by at least one of the methods considered. Interestingly, all methods set all heterogeneous coefficients to zero, suggesting that a single CAD algorithm can be used across all cohorts although different intercepts were used for different disease cohorts. The magnitude of the coefficients from ADeLE largely agree with the published algorithm with most important features being NLP mentions and ICD codes for CAD as well as total number of ICD codes which serves as a measure of healthcare utilization. The SIS-SMA set all variables to zero except for the NLP mentions and ICD codes for CAD while Quad and ADeLE have more similar estimates for the coefficients although Quad also produced slightly sparser model.

Since the true model parameters are unknown, we evaluate the performance of different estimation procedures using the validation data with respect to various classification accuracy
parameters including the area under the receiver operating characteristic curve (AUC), and
$F$-score at threshold value chosen to attain a false positive rate of 5% ($F_{5\%}$) and 10% ($F_{10\%}$),
where the $F$-score is defined as the harmonic mean of the sensitivity and positive predictive
value. The point estimates along with their 95% bootstrap confidence intervals (CIs) of the
accuracy measures using validation data are presented in Figure 3. The results suggest that
ADeLE has the best performance across all methods, nearly on all datasets and across all
measures. Among the integrative methods, SIS-SMA performed much worse than ADeLE
and Quad as seen in simulation studies. Compared to the local estimator and Quad, ADeLE
perform substantially better. For example, the AUC of the CAD algorithm for the RA cohort
trained via ADeLE, Quad, SIS-SMA and local estimation is 0.87 (95% CI [0.84,0.90]), 0.84
(95% CI [0.80,0.87]), 0.77 (95% CI [0.73,0.81]) and 0.83 (95% CI [0.79,0.87]). The difference
between the integrative procedures and the local estimator is more pronounced for the DM
cohort with AUC being around 0.85 for ADeLE and Quad and 0.8 for the local estimator
trained using DM data only. The local estimator fails to produce an informative algorithm
for the MS cohort due to the small size of the training set. These results again demonstrate
the power of borrowing information across studies via integrative analysis.

7. DISCUSSION

In this paper, we proposed a novel approach, the ADeLE, for integrative analysis of high
dimensional data under privacy protection constraint. Although motivated by debiased
LASSO, the ADeLE approach does not require the estimation of the regularized inverse $\hat{\Theta}^{(m)}$
or the debiased estimator $\hat{\beta}_{\text{dlasso}}^{(m)}$ in (5). Our framework differs from the existing distributed
learning literature in that our method accommodates heterogeneity among the design mat-
rices, as well as the coefficients of the local sites. In addition, no existing distributed learning
work provides similar estimation equivalence results as shown in Theorem 2 for LASSO type
estimators in the ultra-high dimensional setting. Challenge in establishing the asymptotic equivalence in Theorem 2 arises from that \( \hat{\beta}^{(0)} \) and \( \hat{\beta}_{\text{ADELE}}^{(0)} \) are not necessarily as sparse as the true coefficient \( \beta_0^{(0)} \). We overcome such challenge by comparing the two estimators in a more elaborative way as detailed in the proof. Moreover, Theorem 3 ensures the sparsity of the ADeLE under some commonly used conditions on deterministic design, and such property is not readily available in the existing literatures for distributed LASSO regression. The ADeLE approach is also efficient both in computation and communication, as it only solves LASSO problem once in each local site without requiring the computation of \( \hat{\Theta}^{(m)} \) or debiasing and only needs one turn in communication.

We assume \( n_m \approx N/M \) in Theorems 1-3 and allow \( M \) to grow slowly (see Remark 7). These conditions seem reasonable in our application but could be violated by some large scale meta-analysis of high dimensional data. The extensions to scenarios with larger \( M \) is highly non-trivial and warrants further research. For the choice of penalty, we focuses primarily on the mixture penalty in the current paper since it is a suitable choice for leveraging the prior assumption on the shared support and magnitude. However, other penalty functions with sparse structures can be incorporated into our framework, such as the composite absolute penalties family (Zhao et al., 2009) and the hierarchical LASSO (Cheng et al., 2015).

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Figure 1: Boxplots of average absolute estimation error (AEE), prediction error (PE), the true positive rate (TPR) and false discovery rate (FDR) associated with identifying $S_\mu$ and $S_\alpha$ based on IPD, ADeLE, Quad, SIS-SMA and SMA when $M = 4$. 
Figure 2: Boxplots of average absolute estimation error (AEE), prediction error (PE), the true positive rate (TPR) and false discovery rate (FDR) associated with identifying $S_\mu$ and $S_\alpha$ based on IPD, ADeLE, Quad, SIS-SMA and SMA when $M = 8$. 

![Boxplots of various metrics](image-url)
Figure 3: Mean and 95% confidence interval of AUC, $F_{5\%}$ and $F_{10\%}$ of ADeLE, SIS-SMA, Quad and Local on the testing data from the four studies.
Table 1: Detected variables and magnitudes of their fitted coefficients for homogeneous effect μ. $A:B$ denotes the interaction term of variables $A$ and $B$. The log$(x + 1)$ transformation is taken on the count data and the covariates are normalized.

| Variable                                      | ADeLE | SIS-SMA | Quad |
|-----------------------------------------------|-------|---------|------|
| Frequency of NLP mention of CAD               | 1.05  | 0.76    | 0.93 |
| ICD codes for CAD                             | 0.66  | 0.19    | 0.52 |
| Total ICD codes                               | -0.61 | (-)     | -0.51|
| Age                                           | 0.18  | (-)     | 0.08 |
| Frequency of NLP mention of non-smoker        | -0.13 | (-)     | -0.12|
| Procedure code for stent or CABG              | 0.05  | (-)     | (-)  |
| Procedure code for Echo                       | -0.04 | (-)     | (-)  |
| ICD codes for hypertension                    | 0.04  | (-)     | (-)  |
| Total ICD codes: Any NLP mention of CAD       | -0.03 | (-)     | (-)  |
| Frequency of NLP mention of CAD procedures    | 0.05  | (-)     | (-)  |
| Prescription codes of statin                  | 0.05  | (-)     | 0.03 |