

HETEROGENEITY-AWARE AND COMMUNICATION-EFFICIENT DISTRIBUTED STATISTICAL INFERENCE

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Abstract

In multicenter research, individual-level data are often protected against sharing across sites. To overcome the barrier of data sharing, many distributed algorithms, which only require sharing aggregated information, have been developed. The existing distributed algorithms usually assume the data are homogeneously distributed across sites. This assumption ignores the important fact that the data collected at different sites may come from various sub-populations and environments, which can lead to heterogeneity in the distribution of the data. Ignoring the heterogeneity may lead to erroneous statistical inference. In this paper, we propose distributed algorithms which account for the heterogeneous distributions by allowing site-specific nuisance parameters. The proposed methods extend the surrogate likelihood approach (Wang et al., 2017; Jordan et al., 2018) to the heterogeneous setting by applying a novel density ratio tilting method to the efficient score function. The proposed algorithms maintain same communication cost as the existing communication-efficient algorithms. We establish the non-asymptotic risk bound of the proposed distributed estimator and its limiting distribution in the two-index asymptotic setting. In addition, we show that the asymptotic variance of the estimator attains the Cramér-Rao lower bound. Finally, the simulation study shows the proposed algorithms reach higher estimation accuracy compared to several existing methods.

KEY WORDS: Data integration; distributed inference; efficient score; surrogate likelihood; two-index asymptotics

1 Introduction

The growth of availability and variety of clinical data has induced the trend of multicenter research (Sidransky et al., 2009). Multicenter research confers many distinct advantages over single-center

studies, including the ability to study rare exposures/outcomes that require larger sample sizes, accelerating the discovery of more generalizable findings, and bringing together investigators who share and leverage resources, expertise, and ideas (Cheng et al., 2017). Since individual-level information is often protected by privacy regularities and rules, directly pooling data across multiple clinical sites is less feasible or requires large amount of operational efforts (Barrows Jr and Clayton, 1996). As a consequence, healthcare systems need more effective tools for evidence synthesis across clinical sites.

Distributed algorithms, also known as the divide-and-conquer procedures, have been applied to multicenter studies. In the classical divide-and-conquer framework, the entire data set is split into multiple subsets and the final estimator is obtained by averaging the local estimators computed using the data from each subset (Li et al., 2013; Chen and Xie, 2014; Lee et al., 2017; Tian and Gu, 2016; Zhao et al., 2016; Lian and Fan, 2017; Battey et al., 2018; Wang et al., 2019). The class of methods adopts the same principle as the meta-analysis in the area of evidence synthesis and systematic review, where the local estimates are combined through a fixed effect or random effects model (DerSimonian and Laird, 1986). When the number of research sites is relatively small, these averaging type of methods are able to perform equally well as the combined analysis using data from all the sites (Hedges, 1983; Olkin and Sampson, 1998; Battey et al., 2018). When the number of research sites is large, as we will demonstrate in the simulation studies, these averaging methods may not be as good as the combined analysis. More importantly, when studying rare conditions, some clinical sites do not have enough number of cases to achieve the asymptotic properties. In such cases, the averaging methods can be suboptimal.

Recently, Wang et al. (2017) and Jordan et al. (2018) proposed a novel surrogate likelihood approach, which approximates the higher order derivatives of the global likelihood by using the likelihood function in a local site. This method has low communication cost and improves the performance of the average method especially when the number of sites is large, see Duan et al. (2019) for a real data application to pharamcoepidemiology. From the practical perspective, the surrogate likelihood approach endowed a highly feasible framework for sharing sensitive data in collaborative environment, especially in biomedical sciences, where the lead investigators often have access to the individual-level data in their home institute, and the collaborative investigators from other sites are willing to share summary statistics but not individual-level information.

Most of the aforementioned distributed algorithms assumed that the data at different sites are independently and identically distributed. However, a prominent concern in multi-center analysis is that there may exist a non-negligible degree of heterogeneity across sites because the samples collected in different sites may come from different sub-populations and environments. One concrete example is the Observational Health Data Sciences and Informatics consortium, which contains over 82 clinical databases from over 20 countries around the world (Hripcsak et al., 2015). The amount of heterogeneity cannot be ignored when implementing distributed algorithms in such healthcare

networks.

In this paper, we aim to fill this methodological gap by extending the distributed algorithms to account for the heterogeneous distributions via allowing site-specific nuisance parameters. In particular, we propose a density-ratio tilted surrogate efficient score approach which only requires the individual-level data from a local site and summary statistics from the other sites. To reduce the influence of estimation of the site-specific nuisance parameters, we propose to use the efficient score function for distributed inference rather than the likelihood as in Jordan et al. (2018). We further adjust for the degree of heterogeneity by applying a novel density ratio tilting method to the efficient score function. We refer the resulting score function as the surrogate efficient score function. The estimator is defined as the root of this function. We show that the communication cost of the proposed algorithm is of the same order as Jordan et al. (2018) assuming no heterogeneity and therefore is communication-efficient. We further establish the nonasymptotic risk bound of the estimator and its limiting distribution in the two-index asymptotic setting. Under mild conditions, the asymptotic variance of the proposed estimator attains the Cramér-Rao lower bound.

To the best of our knowledge, Zhao et al. (2016) is the only work in this area that considers a similar heterogeneous setting. They generalized the divide-and-conquer approach by averaging all the local estimators and studied theoretical properties under the partially linear model. Different from this work, we propose a surrogate efficient score approach under a general parametric likelihood framework. Theoretically, we show that our estimator approximates the global maximum likelihood estimator with a faster rate than the simple average estimator; see Remarks 3 and 4. From the inference perspective, our estimator attains the Cramér-Rao lower bound whereas the simple average estimator has larger asymptotic variance and is not efficient; see Remark 6. We also show that the proposed estimator outperforms the simple average estimator in numerical studies.

2 Wang et al. (2017) and Jordan et al. (2018)’s surrogate likelihood approach for homogenous distributions

In this section, we briefly review the surrogate likelihood approach for distributed inference by Wang et al. (2017) and Jordan et al. (2018). Consider a general parametric likelihood framework, where the random variable Y follows the density function $f(y; \theta)$ indexed by a finite dimensional unknown parameter θ . In the distributed inference problem, we suppose there are K different local sites. Denote $\{Y_{ij}\}$ to be the i -th observation in the j -th site. For notational simplicity, we assume that each site has equal sample size n . The existing works on distributed inference such as Wang et al. (2017) and Jordan et al. (2018) further assume that all the observations are independently and identically distributed across sites, $Y_{ij} \sim f(y; \theta)$. Under this assumption, the combined log

likelihood function can be written as

$$L(\theta) = \frac{1}{Kn} \sum_{j=1}^K \sum_{i=1}^n \log f(y_{ij}; \theta) := \frac{1}{K} \sum_{j=1}^K L_j(\theta),$$

where $L_j(\theta) = \sum_{i=1}^n \log f(y_{ij}; \theta)/n$ is the log-likelihood function obtained at each site. Due to the communication constraint and privacy concerns, one cannot directly combine data across multiple sites to compute the maximum likelihood estimator. Motivated by the following Taylor expansion of the combined likelihood function around some initial value $\bar{\theta}$,

$$L(\theta) = L(\bar{\theta}) + \nabla L(\bar{\theta})^T \theta - \bar{\theta} + \sum_{k=2}^{\infty} \frac{1}{k!} \nabla^k L(\bar{\theta}) (\theta - \bar{\theta})^{\otimes k}, \quad (2.1)$$

Wang et al. (2017) and Jordan et al. (2018) proposed to construct a surrogate likelihood function by approximating all the higher-order derivatives in equation (2.1) using the individual-level data in one of the K sites (such as the first site). When the data are identically and independently distributed across sites, it holds that $\nabla^k L_1(\bar{\theta}) - \nabla^k L(\bar{\theta}) = o_P(1)$ for any $k \geq 2$, where $L_1(\theta)$ is the log-likelihood at the first site. Thus, $\nabla^k L_1(\bar{\theta})$ is an asymptotically unbiased surrogate of $\nabla^k L(\bar{\theta})$. Replacing $\nabla^k L(\bar{\theta})$ with $\nabla^k L_1(\bar{\theta})$, the communication of the higher-order derivatives across sites can be avoided. Hence, by replacing $\sum_{k=2}^{\infty} \nabla^k L(\bar{\theta}) (\theta - \bar{\theta})^{\otimes k} / k!$ with $\sum_{k=2}^{\infty} \nabla^k L_1(\bar{\theta}) (\theta - \bar{\theta})^{\otimes k} / k!$, which also equals to $L_1(\theta) - \nabla L_1(\bar{\theta})^T \theta - \bar{\theta}$ and dropping the terms independent of θ , the surrogate likelihood is defined as

$$\tilde{L}(\theta) := L_1(\theta) + \{\nabla L(\bar{\theta}) - \nabla L_1(\bar{\theta})\}^T. \quad (2.2)$$

The theoretical properties of the maximum surrogate likelihood estimator have been thoroughly studied; see Wang et al. (2017) and Jordan et al. (2018) for details.

3 Surrogate efficient score method for heterogeneous distributions

We consider a heterogeneous setting by assuming the i -th observation in the j -th site Y_{ij} satisfies

$$Y_{ij} \sim f(y; \theta_j), \quad \text{for } i \in \{1, \dots, n\} \text{ and } j \in \{1, \dots, K\},$$

where the unknown parameter θ_j can be decomposed into $\theta_j = (\beta, \gamma_j) \in R^d$. In this partition, β is a p -dimensional parameter of interest assumed to be common in every site, which is the main motivation of evidence synthesis, and the $(d - p)$ -dimensional nuisance parameter γ_j is allowed to be different across sites. The true value of θ_j is denoted by θ_j^* .

If all patient-level data could be pooled together, the combined log-likelihood function is ob-

tained by

$$L_N(\beta, \Gamma) = \frac{1}{Kn} \sum_{j=1}^K \sum_{i=1}^n \log f(y_{ij}; \beta, \gamma_j) := \frac{1}{K} \sum_{j=1}^K L_j(\theta_j),$$

where $L_j(\theta) = \sum_{i=1}^n \log f(y_{ij}; \theta_j)/n$ and $\Gamma = \{\gamma_j\}_{j \in \{1, \dots, K\}} \in R^{(d-p)K}$. In a distributed setting, the surrogate likelihood approach reviewed in Section 2 is not directly applicable due to the following two reasons: the higher order derivatives of the log likelihood function in any site is a biased surrogate of the corresponding higher order derivatives of $L_N(\beta, \Gamma)$, and the total number of nuisance parameters $\dim(\Gamma) = (d-p)K$ increases with sample size n if we allow K to increase with n .

To extend the surrogate likelihood approach to incorporate the site-specific nuisance parameters, we propose to use the efficient score function as a way of reducing the influence of the less accurate estimation of the site-specific γ_j . More specifically, the efficient score function for β is defined as

$$S(\beta, \Gamma) = \frac{1}{Kn} \sum_{j=1}^K \sum_{i=1}^n \left\{ \nabla_{\beta} \log f(y_{ij}; \beta, \gamma_j) - I_{\beta\gamma}^{(j)} I_{\gamma\gamma}^{(j)-1} \nabla_{\gamma} \log f(y_{ij}; \beta, \gamma_j) \right\},$$

where $I_{\gamma\gamma}^{(j)}$ and $I_{\beta\beta}^{(j)}$ are the corresponding submatrices of the information matrix in the j -th site, i.e., $I^{(j)} = \mathbb{E}\{-\nabla^2 L_j(\theta_j^*)\}$.

Instead of constructing a surrogate likelihood function, we aim to construct a surrogate efficient score equation using individual-level data from Site 1, and summary-level data from the other sites. To reduce the complexity of the problem, we first consider an ideal situation where we know the true parameter value γ_j^* . Using the key idea of the surrogate likelihood approach, we aim to construct a function $g^*(y; \beta)$ based on the samples in the first site such that

$$E_{\theta_1^*}\{\nabla_{\beta}^k g^*(Y_{i1}; \beta)\} = E\{\nabla_{\beta}^k S(\beta, \Gamma^*)\}, \quad (3.1)$$

holds for any $k \geq 1$, where we use $E_{\theta_j^*}(\cdot)$ to denote the expectation with respect to the distribution $f(y, \beta^*, \gamma_j^*)$, $E(\cdot)$ to denote the expectation with respect to the the joint distribution of the full data, and Γ^* to denote the true value of Γ . Denote $s_j(Y_{ij}; \beta, \gamma_j) = \nabla_{\beta} \log f(Y_{ij}; \beta, \gamma_j) - I_{\beta\gamma}^{(j)} I_{\gamma\gamma}^{(j)-1} \nabla_{\gamma} \log f(Y_{ij}; \beta, \gamma_j)$. We observe that the right hand side of equation (3.1) can be written as

$$E\{\nabla_{\beta}^k S(\beta, \Gamma^*)\} = \frac{1}{K} \sum_{j=1}^K E_{\theta_j^*}\{\nabla_{\beta}^k s_j(Y_{ij}; \beta, \gamma_j^*)\}.$$

However, the function $g^*(Y_{i1}; \beta)$ only involves samples in the first local site, which follows the distribution $f(y, \beta^*, \gamma_1^*)$ different from $f(y, \beta^*, \gamma_j^*)$ for $j \neq 1$. To achieve equation (3.1), we propose

to construct $g^*(y; \beta)$ by using the density ratio tilting method

$$g^*(y; \beta) = \frac{1}{K} \sum_{j=1}^K \left[\frac{f(y; \beta^*, \gamma_j^*)}{f(y; \beta^*, \gamma_1^*)} \left\{ \nabla_\beta \log f(y; \beta, \gamma_j^*) - I_{\gamma\beta}^{(j)} I_{\gamma\gamma}^{(j)-1} \nabla_\gamma \log f(y; \beta, \gamma_j^*) \right\} \right],$$

where the density ratio $f(y; \beta^*, \gamma_j^*)/f(y; \beta^*, \gamma_1^*)$ is the adjustment that accounts for the heterogeneity of the distributions. We show in Lemma S.11 of the Supplementary Material that $E_{\theta_1^*} \{ \nabla_\beta^k g^*(Y_{i1}; \beta) \} = E \{ \nabla_\beta^k S(\beta, \Gamma^*) \}$ holds for any $k \geq 1$ and observation Y_{i1} in the first local site.

Since $g^*(y; \beta)$ depends on the unknown parameters β^* , γ_j^* and the information matrix $I^{(j)}$, we plug in some initial estimators $\bar{\beta}$ and $\bar{\gamma}_j$ and obtain

$$g(y; \beta, \bar{\beta}, \bar{\Gamma}) = \frac{1}{K} \sum_{j=1}^K \left[\frac{f(y; \bar{\beta}, \bar{\gamma}_j)}{f(y; \bar{\beta}, \bar{\gamma}_1)} \left\{ \nabla_\beta \log f(y; \beta, \bar{\gamma}_j) - \tilde{H}_{\beta\gamma}^{(1,j)} \{ \tilde{H}_{\gamma\gamma}^{(1,j)} \}^{-1} \nabla_\gamma \log f(y; \beta, \bar{\gamma}_j) \right\} \right],$$

where $\tilde{H}_{\beta\gamma}^{(1,j)}$ and $\tilde{H}_{\gamma\gamma}^{(1,j)}$ are the submatrices of $\tilde{H}^{(1,j)}$ defined as

$$\tilde{H}^{(1,j)} = -\frac{1}{n} \sum_{i=1}^n \nabla^2 \log f(y_{i1}; \bar{\beta}, \bar{\gamma}_j) \frac{f(y_{i1}; \bar{\beta}, \bar{\gamma}_j)}{f(y_{i1}; \bar{\beta}, \bar{\gamma}_1)},$$

which is obtained by applying the density ratio tilting method again.

Denote $U_1(\beta; \bar{\beta}, \bar{\Gamma}) = \sum_{i=1}^n g(y_{i1}; \beta, \bar{\beta}, \bar{\Gamma})/n$. Inspired by the definition of the surrogate likelihood defined in equation (2.2), we define the surrogate efficient score function as

$$\tilde{U}(\beta; \bar{\beta}, \bar{\Gamma}) = U_1(\beta; \bar{\beta}, \bar{\Gamma}) + \frac{1}{K} \sum_{j=1}^K \{ \nabla_\beta L_j(\bar{\beta}, \bar{\gamma}_j) - \bar{H}_{\beta\gamma}^{(j)} (\bar{H}_{\gamma\gamma}^{(j)})^{-1} \nabla_\gamma L_j(\bar{\beta}, \bar{\gamma}_j) \} - U_1(\bar{\beta}; \bar{\beta}, \bar{\Gamma}),$$

where $\bar{H}_{\beta\gamma}^{(j)} = \nabla_{\beta\gamma} L_j(\bar{\beta}, \bar{\gamma}_j)$ and $\bar{H}_{\gamma\gamma}^{(j)} = \nabla_{\gamma\gamma} L_j(\bar{\beta}, \bar{\gamma}_j)$.

Recall that $U_1(\beta; \bar{\beta}, \bar{\Gamma})$ is constructed based on the samples in Site 1. Thus the surrogate efficient score only requires to transfer a p -dimensional score vector $S_j(\bar{\beta}, \bar{\gamma}_j) = \nabla_\beta L_j(\bar{\beta}, \bar{\gamma}_j) - \bar{H}_{\beta\gamma}^{(j)} (\bar{H}_{\gamma\gamma}^{(j)})^{-1} \nabla_\gamma L_j(\bar{\beta}, \bar{\gamma}_j)$ from each site together with some initial estimators.

The surrogate efficient score estimator $\tilde{\beta}$ is obtained by solving the following equation for β within Site 1,

$$\tilde{U}(\beta; \bar{\beta}, \bar{\Gamma}) = 0. \quad (3.2)$$

In Section 4, we show that the estimation accuracy of the above estimator $\tilde{\beta}$ can be further improved by iterating the above surrogate efficient score procedures. The method is summarized in the following algorithm. The estimator $\tilde{\beta}$ defined in equation (3.2) is equivalent to the estimator with $T = 1$ in the following algorithm, which is also known as a oneshot procedure.

Remark 1. From an implementation point of view, the broadcast step (line 3) in the above

Algorithm 1 Algorithm for the proposed surrogate efficient score estimator

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1: Set the number of iterations  $T$ 
2: In Site  $j = 1$  to  $j = K$  do
3:   Obtain and broadcast  $(\bar{\beta}_j, \bar{\gamma}_j) = \arg \max_{\beta, \gamma_j} L_j(\beta, \gamma_j)$ ;
4:   Choose a proper weight  $w_j$  and obtain  $\bar{\beta} = \sum_{j=1}^K w_j \bar{\beta}_j / \{\sum_{j=1}^K w_j\}$ ;
5:   Calculate and transfer  $S_j(\bar{\beta}, \bar{\gamma}_j)$  to Site 1;
6: end
7: In Site 1
8:   Construct  $\tilde{U}(\beta; \bar{\beta}, \bar{\Gamma})$  using  $\bar{\beta}$ ,  $\{\bar{\gamma}_j\}$ , and  $\{S_j(\bar{\beta}, \bar{\gamma}_j)\}$ ;
9:   Obtain  $\tilde{\beta}^{(1)}$  by solving  $\tilde{U}(\beta; \bar{\beta}, \bar{\Gamma}) = 0$ ;
10: If  $T = 1$ , output  $\tilde{\beta}^{(1)}$ 
11: If  $T \geq 2$ , for  $t = 2$  to  $t = T$  do
12:   Broadcast  $\bar{\beta}^{(t)} = \tilde{\beta}^{(t-1)}$ ;
13:   In Site  $j = 1$  to  $j = K$  do
14:     Obtain and transfer  $\bar{\gamma}_j^{(t)} = \arg \max_{\gamma_j} L_j(\bar{\beta}^{(t)}, \gamma_j)$  and  $S_j(\bar{\beta}^{(t)}, \bar{\gamma}_j^{(t)})$  to Site 1;
15:   end
16:   In Site 1
17:     Construct  $\tilde{U}(\beta; \bar{\beta}^{(t)}, \bar{\Gamma}^{(t)})$  using  $\bar{\beta}^{(t)}$ ,  $\{\bar{\gamma}_j^{(t)}\}$  and  $\{S_j(\bar{\beta}^{(t)}, \bar{\gamma}_j^{(t)})\}$ ;
18:     Obtain  $\tilde{\beta}^{(t)}$  by solving  $\tilde{U}(\beta; \bar{\beta}^{(t)}, \bar{\Gamma}^{(t)}) = 0$ ;
19:   end
20: Output  $\tilde{\beta}^{(T)}$ 

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algorithm can be done by transferring $\bar{\theta}_j$ from each site to Site 1, and Site 1 returns the initial estimator $\bar{\beta}$ to all the sites. It can also be done by uploading all $\bar{\theta}_j$ to a shared repository and obtaining $\bar{\beta}$ at each site. The initial estimator $\bar{\beta}$ is chosen as a weighted average of the local estimators $\bar{\beta}_j$. When $w_j = 1$ for all j , $\bar{\beta} = \sum_{j=1}^K \bar{\beta}_j / K$ is the simple average estimator (Zhao et al., 2016). We can also choose w_j to be the sample size of each site in the unbalanced design. When w_j is chosen as the inverse of the estimated variance of $\bar{\beta}_j$, the resulting estimator $\bar{\beta}$ is referred to as the fixed effect meta-analysis estimator. In this paper, we simply choose $w_j = 1$. The total communication cost per iteration is to transfer $O(Kd)$ numbers across all sites, where d is the dimension of $\theta_j = (\beta, \gamma_j)$. Comparing to the homogeneous setting, the communication cost is of the same order as Jordan et al. (2018), and is communication-efficient.

Remark 2. To further reduce the computational complexity of solving the surrogate efficient score function, we can approximate the combined efficient score function $S(\beta, \Gamma)$ via one-step Taylor expansion,

$$S(\beta, \Gamma) \approx S(\bar{\beta}, \bar{\Gamma}) + \nabla_{\beta} S(\bar{\beta}, \bar{\Gamma})(\beta - \bar{\beta}) + \nabla_{\Gamma} S(\bar{\beta}, \bar{\Gamma})(\Gamma - \bar{\Gamma}).$$

First, the property of the efficient score implies $\nabla_{\Gamma} S(\bar{\beta}, \bar{\Gamma}) \approx 0$ so that the last term can be neglected. Next, we replace the Hessian matrix $\nabla_{\beta} S(\bar{\beta}, \bar{\Gamma})$ computed by pooling over all the samples with the local surrogate $\nabla_{\beta} \check{U}_1(\bar{\beta})$, where $\check{U}_1(\beta) = U_1(\beta; \bar{\beta}, \bar{\Gamma})$. The resulting linear approximation

$S(\bar{\beta}, \bar{\Gamma}) + \nabla_{\beta} \check{U}_1(\bar{\beta})(\beta - \bar{\beta})$ as an estimating function of β defines the following estimator

$$\tilde{\beta}^O = \bar{\beta} - \{\nabla_{\beta} \check{U}_1(\bar{\beta})\}^{-1} S(\bar{\beta}, \bar{\Gamma}).$$

If we treat $\bar{\beta}$ as an initial estimator, the above estimator $\tilde{\beta}^O$ can be also viewed as a one-step estimator with a local surrogate of the Hessian matrix.

4 Main Results

In this section, we study the theoretical properties of the surrogate efficient score estimator $\tilde{\beta}^{(T)}$ obtained from Algorithm 1. For convenience, we use C, C_1 and C_2 to denote positive constants which can vary from place to place. For sequence $\{a_n\}$ and $\{b_n\}$, we write $a_n \lesssim b_n$ ($a_n \gtrsim b_n$) if there exist a constant C such that $a_n \leq Cb_n$ ($a_n \geq Cb_n$) for all n . We first introduce the following assumptions.

Assumption 1. *The parameter space of β , denoted by \mathcal{B} , is a compact and convex subset of \mathbb{R}^p . The true value β^* is an interior point of \mathcal{B} .*

Assumption 2 (Local Strong Convexity). *Define the expected second-order derivative of the negative log likelihood function to be $I^{(j)}(\theta_j) = E_{\theta_j^*} \{-\nabla^2 \log f(Y_{ij}; \theta_j)\}$. There exist positive constants (μ_-, μ_+) , such that for any $j \in \{1, \dots, K\}$, the population Hessian matrix $I^{(j)}(\theta_j^*)$ satisfies*

$$\mu_- I_d \preceq I^{(j)}(\theta_j^*) \preceq \mu_+ I_d,$$

where I_d is the d dimensional identity matrix. Here, we use the notation that $A \preceq B$ for two matrices A and B if $A - B$ is positive semi-definite.

Assumption 3. *For all $j \in \{1, \dots, K\}$ and $i \in \{1, \dots, n\}$, all components in $\nabla \log f(Y_{ij}, \theta_j^*)$ and $\nabla^2 \log f(Y_{ij}, \theta_j^*)$ are sub-exponential random variables.*

Assumption 4 (Identifiability). *For any $j \in \{1, \dots, K\}$, we denote $F_j(\beta, \gamma_j) = E_{\theta_j^*} \{\log f(Y_{ij}; \beta, \gamma_j)\}$. The parameter (β^*, γ_j^*) is the unique maximizer of $F_j(\beta, \gamma_j)$.*

Assumption 5 (Smoothness). *For each $j \in \{1, \dots, K\}$, let $\bar{\eta}_j = (\bar{\beta}, \bar{\gamma}_1, \bar{\gamma}_j)$, and define*

$$H(\theta_j; y) = \nabla^2 \log f(y; \beta, \gamma_j),$$

and

$$\tilde{H}(\beta, \bar{\eta}_j; y) = \nabla^2 \log f(y; \beta, \bar{\gamma}_j) \frac{f(y; \bar{\beta}, \bar{\gamma}_j)}{f(y; \bar{\beta}, \bar{\gamma}_1)}.$$

Define $U_{\theta}(\rho) = \{\theta; \|\theta - \theta\|_2 \leq \rho\}$ for some radius $\rho > 0$. There exist some function $m_1(y)$ and $m_2(y)$, where $m_1(Y_{ij})$ and $m_2(Y_{ij})$ are sub-exponentially distributed for all $j \in \{1, \dots, K\}$ and

$i \in \{1, \dots, n\}$, such that for any θ_j and $\theta'_j \in U_{\theta_j}(\rho)$, we have

$$\|H(\theta_j; y) - H(\theta'_j; y)\|_2 \leq m_1(y) \|\theta - \theta'_j\|_2.$$

And for any $\beta, \beta' \in U_\beta(\rho)$, $\bar{\eta}_j, \bar{\eta}'_j \in U_{\eta_j}(\rho)$, we have

$$\|\tilde{H}(\beta, \bar{\eta}_j; y) - \tilde{H}(\beta', \bar{\eta}'_j; y)\|_2 \leq m_2(y) \{\|\beta - \beta'\|_2 + \|\bar{\eta}_j - \bar{\eta}'_j\|_2\}.$$

Assumptions 1, 2, 4, and 5 are standard assumptions in the distributed inference literature; see Jordan et al. (2018). Assumption 3 is a general distributional requirements of the data, which covers a wide range of parametric models.

When all individual-level data can be pooled together, the global maximum likelihood estimator $(\hat{\beta}, \hat{\Gamma}) = \arg \max_{\beta, \Gamma} L_N(\beta, \Gamma)$ is considered as the gold standard in practice. The asymptotic property of the global estimator has been studied in Li et al. (2003) under the asymptotic regime $K/n \rightarrow c \in (0, \infty)$. Our first result characterizes a non-asymptotic bound for the distance between the global maximum likelihood estimator $\hat{\beta}$ and the true parameter value β^* .

Lemma 1. *Under Assumptions 1-5, the global maximum likelihood estimator $\hat{\beta}$ satisfies*

$$E\|\hat{\beta} - \beta^*\|_2 \leq \frac{C_1}{(Kn)^{1/2}} + \frac{C_2}{n}$$

for some positive constants C_1 and C_2 not related to n and K .

To the best of our knowledge, this is one of the first nonasymptotic results on the rate of convergence of the maximum likelihood estimator in the presence of site-specific nuisance parameters. Under the classical two-index asymptotics setting, we allow the number of sites K to grow with the sample size n . As a result, the dimension of nuisance parameters Γ also increases with n . Let $N = Kn$ denote the total sample size. This lemma implies that the convergence rate of $\hat{\beta}$ is of order $O_p(N^{-1/2})$ when $K/n = O(1)$, which attains the optimal rate of convergence with known nuisance parameters. However, when $K/n \rightarrow \infty$, the estimator has a slower rate $O_p(1/n)$. In particular if n is fixed, the global maximum likelihood estimator is no longer consistent, which is known as the Neyman-Scott problem (Neyman et al., 1948).

In the following, we characterize the difference between the proposed estimator and the maximum likelihood estimator $\hat{\beta}$. We first focus on the estimator $\tilde{\beta}$ defined in equation (3.2), which is identical to $\tilde{\beta}^{(1)}$ in algorithm 1 with the number of iterations $T = 1$.

Theorem 1. *Suppose Assumptions 1-5 hold. In Algorithm 1, if the number of iterations $T = 1$, assuming $n \gtrsim \log K$, we have*

$$\mathbb{E}\|\tilde{\beta}^{(1)} - \hat{\beta}\|_2 \leq \frac{C}{n}.$$

where C is a positive constant not related to n and K .

The above theorem shows that the proposed estimator with only one iteration converges to the global estimator $\hat{\beta}$ with a rate only depending on n . Together with Lemma 1, we obtain $\mathbb{E}\|\tilde{\beta}^{(1)} - \beta^*\|_2 \lesssim 1/(Kn)^{1/2} + 1/n$. In other words, the estimator has the same rate of convergence as the global maximum likelihood estimator.

Remark 3. When $K/n \rightarrow 0$, we showed in Lemma S.10 of the Supplementary material that the simple average estimator $\bar{\beta}^{(1)} = \sum_{j=1}^K \bar{\beta}_j^{(1)}/K$ defined in algorithm 1 satisfies $\mathbb{E}\|\bar{\beta}^{(1)} - \hat{\beta}\|_2 \gtrsim 1/(Kn)^{1/2}$. By comparing with the bound in Theorem 1, we have

$$\mathbb{E}\|\tilde{\beta}^{(1)} - \hat{\beta}\|_2 \leq C \left(\frac{K}{n}\right)^{1/2} \mathbb{E}\|\bar{\beta}^{(1)} - \hat{\beta}\|_2. \quad (4.1)$$

Thus our estimator $\tilde{\beta}^{(1)}$ is closer to the global maximum likelihood estimator than the simple average estimator under the condition $K/n \rightarrow 0$.

Our next result shows that after at least one iteration the estimator $\tilde{\beta}^{(T)}$ in algorithm 1 with $T \geq 2$ has a tighter bound than $\tilde{\beta}^{(1)}$ in Theorem 1. This explains why we advocate the iterative algorithm 1 in Section 3.

Theorem 2. Suppose all the assumptions in Theorem 1 hold. In Algorithm 1, if the number of iterations $T \geq 2$, we have

$$\mathbb{E}\|\tilde{\beta}^{(T)} - \hat{\beta}\|_2 \leq \frac{C_1}{(K)^{1/2}n} + \frac{C_2}{n^{3/2}},$$

where C_1 and C_2 are positive constants not related to n and K .

Remark 4. The above theorem implies that when $K/n \rightarrow 0$, for any $T \geq 2$

$$\mathbb{E}\|\tilde{\beta}^{(T)} - \hat{\beta}\|_2 \leq Cn^{-1/2}\mathbb{E}\|\bar{\beta}^{(1)} - \hat{\beta}\|_2, \quad (4.2)$$

which improves the result in equation (4.1). When K is relatively small, our estimator $\tilde{\beta}^{(T)}$ with $T \geq 2$ is closer to the global maximum likelihood estimator by a factor of $n^{-1/2}$ than the simple average estimator. We also see an interesting fact that the dimension of the nuisance parameters has no effect on the relative error $\mathbb{E}\|\tilde{\beta}^{(T)} - \hat{\beta}\|_2/\mathbb{E}\|\bar{\beta}^{(1)} - \hat{\beta}\|_2$. This dimension-free phenomenon provides an explanation of why the proposed estimator consistently outperforms the simple average method in our simulation studies in Section 6.

Our next theorem establish the asymptotic normality of the proposed estimator.

Theorem 3. Suppose all the assumptions in Theorem 1 hold. Define $I_{\beta|\gamma} = \sum_{j=1}^K I_{\beta|\gamma}^{(j)}/K$, where $I_{\beta|\gamma}^{(j)}$ is the partial information matrix of β defined as $I_{\beta|\gamma}^{(j)} = I_{\beta\beta}^{(j)} - I_{\beta\gamma}^{(j)}(I_{\gamma\gamma}^{(j)})^{-1}I_{\gamma\beta}^{(j)}$. Assuming

$K = cn^r$ for some fixed $r \in [0, 1)$, we have for any $T \geq 1$, as $n \rightarrow \infty$,

$$Kn(\tilde{\beta}^{(T)} - \beta^*)_{\beta|\gamma}^T (\tilde{\beta}^{(T)} - \beta^*) \rightarrow \chi_p^2.$$

To obtain the \sqrt{Kn} -asymptotic normality of the proposed estimator $\tilde{\beta}^{(T)}$, we have to restrict to the setting $K = Cn^r$ for some $r \in [0, 1)$. In particular, when $K/n \rightarrow C \in (0, \infty)$ or equivalently $r = 1$, Li et al. (2003) showed that the maximum likelihood estimator $\hat{\beta}$ is asymptotically biased, that is $(Kn)^{1/2} I_{\beta|\gamma}^{1/2}(\hat{\beta} - \beta^*) \rightarrow N(b, I_p)$, for some $b \neq 0$. Since the proposed estimator $\tilde{\beta}^{(T)}$ (with $T \geq 2$) satisfies $\tilde{\beta}^{(T)} - \hat{\beta} = O_p(K^{-1/2}n^{-1} + n^{-3/2})$ by Theorem 2, it implies that the same asymptotic distribution holds for $\tilde{\beta}^{(T)}$, $(Kn)^{1/2} I_{\beta|\gamma}^{1/2}(\tilde{\beta}^{(T)} - \beta^*) \rightarrow_d N(b, I_p)$ for the same $b \neq 0$ if $r = 1$. The same limiting distribution also holds for $T = 1$. This leads to a phase transition of the limiting distribution of $\tilde{\beta}^{(T)}$ at $r = 1$. As a result, the condition $r \in [0, 1)$ is essential for the asymptotic unbiasedness of $\tilde{\beta}^{(T)}$ and cannot be further relaxed.

Remark 5. The choice of the initial value $\bar{\theta}_j^{(1)}$ in line 3 of Algorithm 1 is not necessarily restricted to the local maximum likelihood estimator. Due to the use of the efficient score, the impact of the initial estimators of the nuisance parameters is alleviated. We can show that the conclusions of Theorem 1-3 still hold if $\bar{\theta}_j^{(1)}$ is replaced with any \sqrt{n} -consistent estimator.

It is well known that the simple average estimator is fully efficient under the homogeneous setting; see e.g., Battey et al. (2018) and Jordan et al. (2018). However, the following proposition shows that this estimator is no longer efficient under the considered heterogeneous setting.

Proposition 1. Recall that the simple average estimator is $\bar{\beta} = \sum_{j=1}^K \bar{\beta}_j / K$, where $(\bar{\beta}_j, \bar{\gamma}_j) = \arg \max_{\beta, \gamma_j} L_j(\beta, \gamma_j)$. Suppose all the conditions in Theorem 3 hold. We have as $n \rightarrow \infty$,

$$Kn(\bar{\beta} - \beta^*)^T \left\{ \frac{1}{K} \sum_{j=1}^K I_{\beta|\gamma}^{(j)-1} \right\}^{-1} (\bar{\beta} - \beta^*) \rightarrow \chi_p^2.$$

Remark 6. In this remark, we compare the asymptotic variance of $\tilde{\beta}^{(T)}$ in Theorem 3 and $\bar{\beta}$ in Proposition 1. Our proposed estimator $\tilde{\beta}^{(T)}$ is efficient in the sense that its asymptotic variance is equal to the Cramér-Rao lower bound, i.e., $\lim_{K \rightarrow \infty} I_{\beta|\gamma} = \lim_{K \rightarrow \infty} \{\sum_{j=1}^K I_{\beta|\gamma}^{(j)} / K\}^{-1}$, for any $T \geq 1$. On the other hand, the simple average estimator is not efficient as its asymptotic variance because $\lim_{K \rightarrow \infty} \sum_{j=1}^K I_{\beta|\gamma}^{(j)-1} / K \succeq \lim_{K \rightarrow \infty} I_{\beta|\gamma}^{-1}$.

Finally, to construct the confidence interval of β^* , we need to provide a consistent estimator for the averaged partial information matrix $I_{\beta|\gamma}$. In the following theorem, we apply the density ratio tilting approach to estimate the variance using data only from the first local site.

Theorem 4. Suppose all the assumptions in Theorem 3 hold. Define

$$\tilde{I}^{(j)} = -\frac{1}{Kn} \sum_{j=1}^K \sum_{i=1}^n \frac{f(y_{i1}, \tilde{\beta}^{(T)}, \tilde{\gamma}_j^{(T)})}{f(y_{i1}, \tilde{\beta}^{(T)}, \tilde{\gamma}_1^{(T)})} \nabla^2 \log f(y_{i1}; \tilde{\beta}^{(T)}, \tilde{\gamma}_j^{(T)}),$$

and $\tilde{I}_{\beta|\gamma}^{(j)} = \tilde{I}_{\beta\beta}^{(j)} - I_{\beta\gamma}^{(j)}(\tilde{I}_{\gamma\gamma}^{(j)})^{-1}\tilde{I}_{\gamma\beta}^{(j)}$. We have as $n \rightarrow \infty$,

$$Kn(\tilde{\beta}^{(T)} - \beta^*)^T(\tilde{\beta}^{(T)} - \beta^*) \rightarrow \chi_p^2.$$

5 Reduce the influence of the local site

In a practical collaborative research network, each site can act as the local site and obtain an estimate using Algorithm 1. To further reduce the impact of the choice of the local site and improve the stability of the algorithm, we can combine these estimates in Algorithm 1 by a simple average. At the j -th site, we define the site-specific surrogate score function to be

$$\tilde{U}_j(\beta; \bar{\beta}, \bar{\Gamma}) = U_j(\beta; \bar{\beta}, \bar{\Gamma}) + \frac{1}{K} \sum_{k=1}^K \{ \nabla_{\beta} L_k(\bar{\beta}, \bar{\gamma}_k) - \bar{H}_{\beta\gamma}^{(k)}(\bar{H}_{\gamma\gamma}^{(k)})^{-1} \nabla_{\gamma} L_k(\bar{\beta}, \bar{\gamma}_k) \} - U_j(\bar{\beta}; \bar{\beta}, \bar{\Gamma}),$$

where

$$U_j(\beta; \bar{\beta}, \bar{\Gamma}) = \frac{1}{Kn} \sum_{k=1}^K \sum_{i=1}^n \frac{f(y_{ij}; \bar{\beta}, \bar{\gamma}_k)}{f(y_{ij}; \bar{\beta}, \bar{\gamma}_j)} \left\{ \nabla_{\beta} \log f(y_{ij}; \beta, \bar{\gamma}_k) - \tilde{H}_{\beta\gamma}^{(j,k)} \{ \tilde{H}_{\gamma\gamma}^{(j,k)} \}^{-1} \nabla_{\gamma} \log f(y_{ij}; \beta, \bar{\gamma}_k) \right\}$$

and

$$\tilde{H}^{(j,k)} = -\frac{1}{n} \sum_{i=1}^n \nabla^2 \log f(y_{ij}; \bar{\beta}, \bar{\gamma}_k) \frac{f(y_{ij}; \bar{\beta}, \bar{\gamma}_k)}{f(y_{ij}; \bar{\beta}, \bar{\gamma}_j)}.$$

The surrogate score function $\tilde{U}_j(\beta; \bar{\beta}, \bar{\Gamma})$ is obtained using the individual-level data in the j -th site and summary-level data from the other $K - 1$ sites. In this case, each site can obtain a surrogate efficient score estimator $\tilde{\beta}_j$ by solving $\tilde{U}_j(\beta; \bar{\beta}, \bar{\Gamma}) = 0$, and we further combine these estimators by $\tilde{\beta}_{all} = \sum_{j=1}^K \tilde{\beta}_j / K$. The variance of $\tilde{\beta}_{all}$ can be estimated by $\tilde{V} = \{ \sum_{j=1}^K \tilde{I}_j^K \}^{-1}$. The algorithm is summarized below.

6 Simulation Study

We consider a logistic regression between a binary outcome Y and a binary exposure X , controlling for a confounding variable Z . It is assumed that for data in the k -th site, we have

$$\text{logit}\{Pr(Y = 1 | X, Z)\} = \gamma_{0k} + \beta X + \gamma_{1k} Z.$$

Algorithm 2 Algorithm for the proposed surrogate efficient score estimator

```
1: In Site  $j = 1$  to  $j = K$  do
2:   Obtain an initial estimator  $\bar{\theta}_j = (\bar{\beta}_j, \bar{\gamma}_j)$  for the parameter  $\beta$  and  $\gamma_j$ ;
3:   Broadcast  $\bar{\theta}_j$ ;
4:   Choose  $w_j^{(1)}$  and obtain  $\bar{\beta}^{(1)} = \sum_{j=1}^K w_j^{(1)} \bar{\beta}_j / \{\sum_{j=1}^K w_j^{(1)}\}$ ;
5:   Obtain and broadcast  $S_j(\bar{\beta}, \bar{\gamma}_j)$ ;
6:   Construct  $\tilde{U}_j(\beta; \bar{\beta}, \bar{\Gamma})$  using  $\bar{\beta}$ ,  $\{\bar{\gamma}_j\}$  and  $\{S_k(\bar{\beta}, \bar{\gamma}_k)\}_{1 \leq k \leq K}$ ;
7:   Obtain  $\tilde{\beta}_j$  by solving  $\tilde{U}_j(\beta; \bar{\beta}, \bar{\Gamma}) = 0$ ;
8:   Broadcast  $\tilde{\beta}_j$ ;
9: end
10: Obtain  $\tilde{\beta}_{all} = \sum_{j=1}^K \tilde{\beta}_j / K$ 
11: Output  $\tilde{\beta}_{all}$ 
```

We set the true value of $\beta = -1$ for all the K sites. The nuisance parameters γ_{0k} and γ_{1k} are generated from the normal distribution $N(a, 1)$ and the uniform distribution $U(-2, 2)$, respectively. The binary exposure X is generated from a Bernoulli distribution with probability b , and the confounder variable is generated by $Z \sim N(X - 0.3, 1)$. By varying the value of a and the probability b , we are able to control the prevalence of the exposure and the outcome. We consider the following four scenarios: (1) both the outcome and the exposure are common; (2) the outcome is rare and the exposure is common; (3) the outcome is common and the exposure is rare; (4) both the outcome and the exposure are rare. The parameter values for a and b are presented in Table 1. Under each setting, we set the sample size n to be 100 and the number of sites K to be 10 or 50. We compare the performance of five different methods: (1) The estimator from averaging all local maximum likelihood estimators (Average); (2) The surrogate likelihood method in Jordan et al. (2018) assuming the homogeneous model (Homo); (3) The proposed estimator in Algorithm 1 with $T = 1$ (i.e., the oneshot algorithm) (M1); (4) The proposed estimator in Algorithm 1 with $T = 2$ (M2), and (5) The proposed estimator in Algorithm 2 (M3).

Figure 1 and Figure 2 plot the estimates from the five methods when the number of sites K is 10 and 50 across 1000 replications, respectively. We observe that the surrogate likelihood method which ignores the heterogeneity has substantial bias in all settings. When both the outcome and exposure are common, all the proposed estimators and the average estimator perform well. The average estimator starts to show large bias when either the outcome or the exposure is rare. In particular, when both the outcome and the exposure are rare, we observe grossly large bias around -10 to -13 from the average estimator. Our oneshot estimator (M1) reduces the bias of the average estimator in all settings. However, when both outcome and exposure are rare, the oneshot algorithm illustrates non-negligible bias and relatively large variation. Through only one more iteration, our estimator (M2) has sizeably improved performance and becomes more stable in the rare outcome or exposure setting. The estimator in Algorithm 2 (M3) also outperforms the oneshot method in

Table 1: Parameter values for four simulation settings

	Common Outcome	Rare Outcome
Common Exposure	$a = -1$ (outcome prevalence: 0.43) $b = 0.3$ (exposure prevalence: 0.3)	$a = -3$ (outcome prevalence: 0.06) $b = 0.3$ (exposure prevalence: 0.3)
Rare Exposure	$a = -1$ (outcome prevalence: 0.45) $b = 0.1$ (exposure prevalence: 0.1)	$a = -3$ (outcome prevalence: 0.07) $b = 0.1$ (exposure prevalence: 0.1)

terms of reducing the bias and variance, especially when both the outcome and the exposure are rare. When we increase the number of sites, the bias of the average method remains the same while the variation is smaller. Our proposed algorithms, however, are able to take advantage of the increased total sample size and provide estimates with smaller bias.

In summary, the simulation study suggests that the proposed distributed algorithms can effectively account for between-site heterogeneity and lead to relatively accurate estimation.

7 Discussion

Motivated from a practical consideration that the data stored at different clinical sites are often heterogeneously distributed, we propose a surrogate efficient score approach for distributed inference. Our approach provides flexibility to allow site-specific nuisance parameters, and bridges the gap in the current research on healthcare distributed research networks. There are several future research directions. To account for the large number of clinical, environmental and genetic related variables in the modern healthcare datasets, it will be interesting to extend our method to the high-dimensional settings where either the dimension of β or the dimension of the nuisance parameters is larger than the sample size. Moreover, to extend the scope of the proposed framework, it would be of interest to relax the parametric assumption by using methods such as the generalized estimating equations (Liang and Zeger, 1986) and the generalized methods of moments (Hansen, 1982). However, as the density ratio tilting relies on the distributional assumption, it may require new methodological development to adjust for the heterogeneity under these new settings. These topics are currently under investigation and will be reported in the future.

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Figure 1: Boxplots of the estimates (subtracted by the true parameter value) from the comparing methods under the four parameter settings in Table 1. The number of sites K is set to 10, each site has a sample size 100, and each setting is replicated 1000 times.

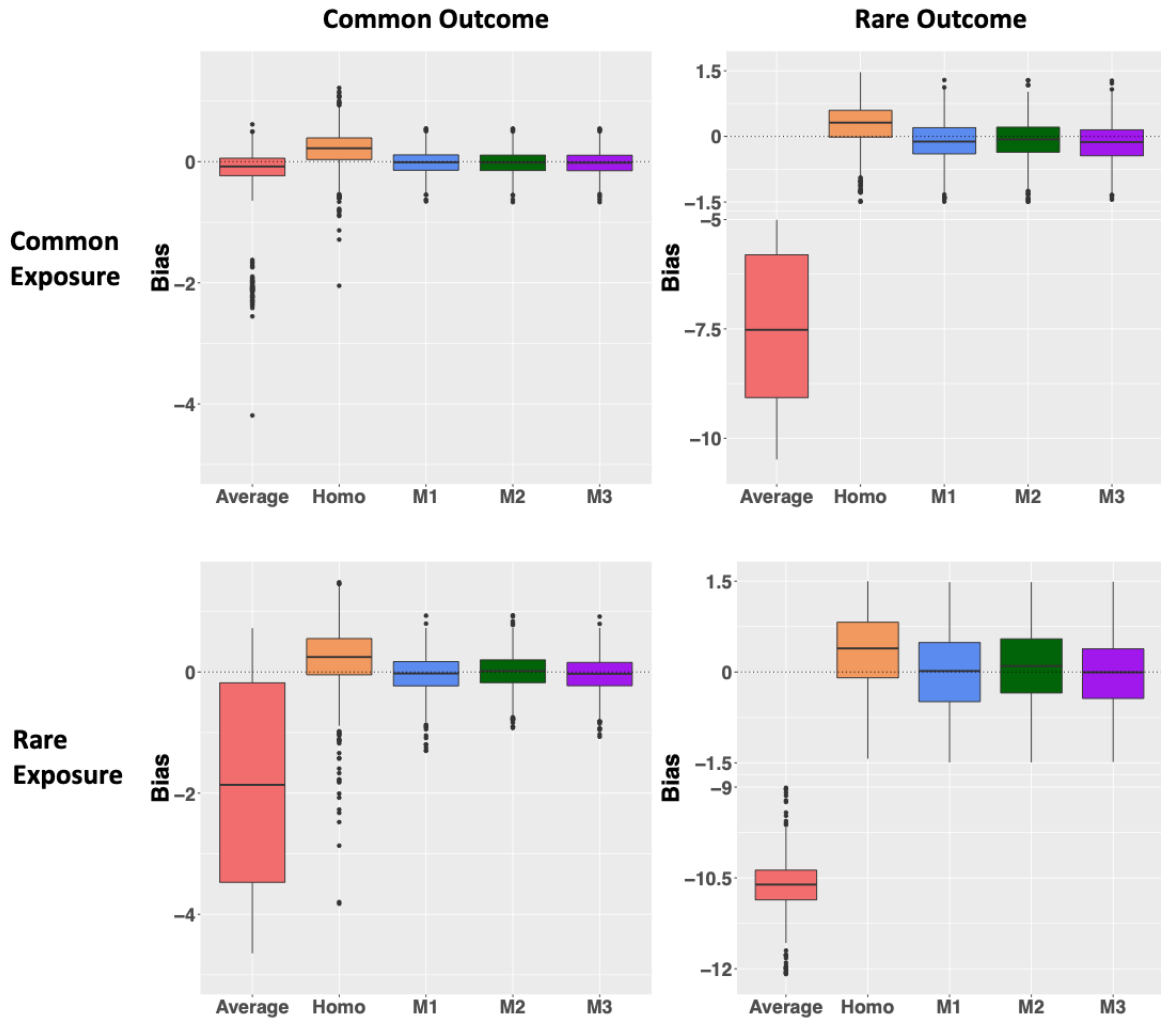


Figure 2: Boxplots of the estimates (subtracted by the true parameter value) from the comparing methods under the four parameter settings in Table 1. The number of sites K is set to 50, each site has a sample size 100, and each setting is replicated 1000 times.

