Abstract

In microbiome and genomic study, the regression of compositional data has been a crucial tool for identifying microbial taxa or genes that are associated with clinical phenotypes. To account for the variation in sequencing depth, the classic log-contrast model is often used where read counts are normalized into compositions. However, zero read counts and the randomness in covariates remain critical issues.

In this article, we introduce a surprisingly simple, interpretable, and efficient method for the estimation of compositional data regression through the lens of a novel high-dimensional log-error-in-variable regression model. The proposed method provides both corrections on sequencing data with possible overdispersion and simultaneously avoids any subjective imputation of zero read counts. We provide theoretical justifications with matching upper and lower bounds for the estimation error. We also consider a general log-error-in-variable regression model with corresponding estimation method to accommodate broader situations. The merit of the procedure is illustrated through real data analysis and simulation studies.
Keywords: compositional data, error-in-variable, high-dimensional regression, microbiome study, minimax optimality

1 Introduction

Motivated by an array of applications, high-dimensional regression has attracted enormous attention in contemporary research. The canonical model of high-dimensional regression can be written as \( y = X\beta^* + \varepsilon \), where \( y = (y_1, \ldots, y_n)\top \) is the response vector, \( X \in \mathbb{R}^{n \times p} \) is the covariate matrix, and \( \beta^* \in \mathbb{R}^p \) is the unknown coefficient vector of interest. When sample size \( n \) is much smaller than the number of available predictor \( p \), but larger than the number of relevant parameters \( s \), one can perform various well-established methods, such as Lasso (Tibshirani, 1996), SCAD (Fan and Li, 2001), and Dantzig selector (Candes and Tao, 2005) among others, to estimate \( \beta^* \).

Much prior attention to high-dimensional regression focused on the “clean data” case where the covariates are accurately observed. However, in applications of econometrics (Greene, 2003), genomics (Purdom and Holmes, 2005; Cao et al., 2017), and engineering (Slijepcevic et al., 2002), we also frequently see covariates corrupted with noise. Previous literature referred to such scenarios as “error-in-variable” and showed that performing standard regression methods directly on the corrupted covariates may yield inaccurate inference results (Hausman, 2001). When the observable covariates are corrupted by additive Gaussian or sub-Gaussian noises, the methods and theories for error-in-variable regression have been widely considered previously. For example, to adjust for the bias of regular least square estimator in the low-dimensional setting, various methods, e.g., Deming regression (Deming, 1943) and method of moments (Pal, 1980), were introduced. In more recent high-dimensional settings, Rosenbaum and Tsybakov (2010), Rosenbaum and Tsybakov (2013) and Belloni et al. (2016b) introduced matrix uncertainty selectors and their improved versions, and proposed to solve by linear or conic programming; Belloni et al. (2017a, b) further studied the confidence band and pivotal estimation, respectively; Loh and Wainwright (2012) introduced unbiased surrogates for \( XX\top \) and \( y\top X \) and cast the estimation into non-convex
optimization problems; Datta and Zou (2017) proposed convex conditioned Lasso estimator under additive and multiplicative noise settings; recently, Rudelson et al. (2017) discussed the regression with correlated error-in-variables.

The focus of high-dimensional error-in-variable regression has so far been mainly on homoskedastic Gaussian, sub-Gaussian, or bounded corruption setting. Motivated by applications in high-throughput sequencing in microbiome studies, we consider a new framework of high-dimensional error-in-variable regression that adapts to compositional covariates in this paper. Before detailed explanations, we first discuss the background of microbiome data analysis and the setup of high-dimensional log-contrast model with sequencing data.

1.1 Regression Analysis for Microbial Compositional Data

The human microbiome is the aggregate of all microbes that reside on human bodies. It has attracted enormous recent attention due to its association with human health (The Human Microbiome Project Consortium, 2012). Recent studies found that human microbiome may be closely related with various diseases, such as cancer (Schwabe and Jobin, 2013), Crohn’s disease (Lewis et al., 2015), and obesity (Turnbaugh et al., 2006, 2009). Modern next-generation sequencing technologies, such as 16S ribosomal RNA and shotgun metagenomics sequencing, provide quantification of the human microbiome by performing direct DNA sequencing on either whole metagenomes or individual marker genes. By aligning sequence reads to referential microbial genomes, we can organize the sequencing data into a count matrix with rows representing samples and columns representing microbial taxa or genes. Such data can be seen as the random realization of relative abundance of bacteria in each sample.

To account for the difference in sequencing depth, i.e., total read count, across samples (see Li (2015) for a survey and the references therein), the sequencing read counts of bacterial genes are often normalized into compositions. The resulting data, also called compositional data, pose statistical challenges due to the collinearity and non-normality that come from their compositional nature. To address these issues, Aitchison and Bacon-shone (1984)
introduced the log-contrast model:
\[
y_i = \sum_{j=1}^{p-1} \log(Z_{ij}/Z_{ip})\beta_j^* + \varepsilon_i, \quad i = 1, \ldots, n.
\] (1)

Here, \( W_{ij} \) and \( Z_{ij} = W_{ij}/(\sum_{j=1}^{p} W_{ij}) \) are the absolute count and the relative abundance of the \( j \)th component (e.g. bacterial gene or taxon) in the \( i \)th sample, respectively; \( y = (y_1, \ldots, y_n)^\top \) is the regression response; \( \varepsilon = (\varepsilon_1, \ldots, \varepsilon_n)^\top \) is the noise; \( n \) is the sample size and \( p \) is the number of components. The analysis of log-contrast model (1) is often dependent on the choice of reference component \( Z_{ip} \), especially in high-dimensional settings. To address this issue, Lin et al. (2014) reformulated (1) by introducing \( \beta_p^* = -\sum_{j=1}^{p-1} \beta_j^* \),
\[
y_i = \sum_{j=1}^{p} \log(Z_{ij})\beta_j^* + \varepsilon_i, \quad i = 1, \ldots, n, \quad \text{subject to } \sum_{j=1}^{p} \beta_j^* = 0
\] (2)
and estimated \( \beta^* \) through constrained \( l_1 \) regularized estimator
\[
\hat{\beta} = \arg\min_{\beta: \sum_{j} \beta_j = 0} \left\{ \frac{1}{2n} \sum_{i=1}^{n} \left( y_i - \sum_{j=1}^{p} \log(Z_{ij})\beta_j \right)^2 + \lambda||\beta||_1 \right\}. \tag{3}
\]

More recently, Shi et al. (2016) studied the statistical inference and confidence intervals for \( \beta^* \), Wang and Zhao (2017) considered the subcomposition selection in compositional data regression via a tree-guided regularization method, and Lu et al. (2018) investigated the logistic regression of compositional data.

The direct application of Models (1) and (2) by normalizing sequencing read counts, i.e., using \( Z_{ij} = W_{ij}/(\sum_{j=1}^{p} W_{ij}) \) as covariates, has several drawbacks. Firstly, it ignores the fact that \( Z_{ij} \)’s are random realizations rather than true compositions of the components. In next-generation sequencing data, \( Z_{ij} \) is the proportion of read count of component \( j \) among all components in sample \( i \), and is thus a transformation of discrete random variables that reflect the underlying true compositions with measurement errors. As mentioned earlier, overlooking the measurement error in regressors may lead to inaccurate results. By treating \( Z_{ij} \) as the true compositions, it is also overlooking the heteroskedasticity or overdispersion of \( Z_{ij} \) caused by enormous uncontrollable factors of variation in sequencing, e.g., time, sampling location, or technical variability (Chen and Li, 2013). Secondly, the procedure requires \( Z_{ij} > 0 \) while in reality, compositional data from next-generation sequencing often contain
a lot of zeros due to rarity of certain components. Strategies to deal with the zeros include replacing zero counts by a subjectively chosen small number, such as 0.5, before normalizing counts into compositions (Aitchison, 2003; Martin-Fernandez et al., 2000; Martín-Fernández et al., 2003, 2015), or imputing the entire composition matrix (Cao et al., 2017) based on low-rank assumption. However, to the best of our knowledge, there is still no consensus on the best approach to deal with zero read counts in compositional data regression.

### 1.2 High-Dimensional Log-Error-in-Variable Regression

To address the aforementioned problems in compositional data regression, we introduce a high-dimensional log-error-in-variable regression model that directly handles count covariates without normalization into compositions or imputation of zeros. Recall $W_{ij}$ is the count of the $j$th component in the $i$th sample. We assume $W_i = (W_{i1},\ldots,W_{ip})^\top$ to satisfy Dirichlet-multinomial distribution (Mosimann, 1962) given the total count $N_i = \sum_{j=1}^{p} W_{ij}$ in the $i$th sample,

$$W_i|N_i \sim \text{Dirichlet-Multinomial}(N_i,\alpha_iX_{i1},\ldots,\alpha_iX_{in}).$$  (4)

where $N_i$ follows Poisson($\nu_i$) to account for the randomness of sequencing depth, $X_i = (X_{i1},\ldots,X_{ip})^\top$ is the underlying true composition of the $p$ components, and $\alpha_i$ is the overdispersion parameter of the subject from which the $i$th sample is measured. When $\alpha_i$ goes to infinity, the Dirichlet-multinomial distribution degenerates to the regular multinomial distribution. More detailed discussions on Dirichlet-multinomial distribution is given in Section 2.

Since observable counts $W_i$ are merely realizations of underlying compositions $X_i$, it is more reasonable to assume association between $y_i$ and $X_i$s rather than between $y_i$ and $W_i$s. We thus assume the regression response $y_i$ to be dependent on $X_i$s through the following log-contrast model,

$$y_i = \sum_{j=1}^{p} \log(X_{ij})\beta_j^* + \varepsilon_i, \quad i = 1,\ldots,n, \quad \text{subject to} \quad \sum_{j=1}^{p} \beta_j^* = 0. \quad (5)$$

We refer to (4) together with (5) as log-error-in-variable regression model, which is well-suited for regression with read count covariates in microbial studies. Our aim is to estimate
Based on responses \( y \in \mathbb{R}^n \) and error-in-covariates \( W \in \mathbb{R}^{n \times p} \). Most of the results on error-in-variables regression, e.g., [Rosenbaum and Tsybakov (2010, 2013); Belloni et al. (2016a,b); Datta and Zou (2017)], deal with homoscedastic continuous variables and may not be directly applied here since the \( W_i \)'s are discrete random variables with heteroscedasticity depending on \( X_i \) and \( \alpha_i \). Therefore, new methods are in need for the estimation of log-error-in-variable model.

In this paper, we propose a surprisingly simple and straightforward estimation scheme, named variable correction regularized estimator, for the high-dimensional log-error-in-variable regression. In particular, when the count observations are without overdispersion, we propose to add 0.5 to all counts \( W_{ij} \), then estimate the regression parameters using constrained Lasso; for overdispersed data, we propose to add an amount related to the overdispersion level to \( W_{ij} \) to alleviate the effect of any overly large or small counts due to overdispersion. We show that the proposed methods achieves minimax optimal performance in a general class of settings.

In addition, we consider a more general log-error-in-variable regression model to accommodate broader types of settings.

\[
y_i = \sum_{j=1}^{p} \log(\nu_{ij}) \beta_j^* + \varepsilon_i, \quad i = 1, \ldots, n, \quad \text{subject to} \quad C^\top \beta^* = 0, \quad W_{ij} \sim \mathbb{P}_{\nu_{ij}} \text{ independently.} \tag{6}
\]

Here, \( \mathbb{P}_{\nu_{ij}} \) is a general class of distributions with mean parameter \( \nu_{ij} \), \( \varepsilon_i \) are i.i.d. sub-Gaussian noises with mean zero and variance \( \sigma^2 \), and \( C \) is a \( p \times r \) matrix with each column representing a linear constraint on the regression coefficients. We provide the variable correction regularized estimator for \( \beta^* \) in (6) with theoretical guarantees.

### 1.3 Organization of the Paper

The rest of the article is organized as follows. In Section 2, we introduce the variable correction regularized estimator under the high-dimensional log-error-in-variable regression model described by (4) and (5). In Section 3, we provide theoretical guarantee for the estimation accuracy when overdispersion is present and absent, respectively. In Section
we discuss the more general error-in-variable model (6), for which we provide both an estimation procedure and theoretical analysis. A real data application in a longitudinal human gut microbiome study is presented in Section 5.1 Simulation results are provided in Section 5.2 Finally, we collect the proofs in Section 7 and the supplementary materials.

2 Methods for Log-Error-in-Variable Regression

We first introduce the notations that will be used in this paper. For any vector $v$, let $\|v\|_q = (\sum_i |v_i|^q)^{1/q}$ be the $\ell_q$ norm. Especially, $\|v\|_\infty = \max_i |v_i|$. Let $1_p$ be the $p$-dimensional vector with all entries as ones. We use boldface letters, such as $W, C$, to denote matrices. Let $I_p$ be the $p$-by-$p$ identity matrix. For any matrix $W$, define $\|W\|_q = \max_v \|Wv\|_q/\|v\|_q$ to be the $\ell_q$ operator norm of $W$. The uppercase $C$, lowercase $c$, and their variations, e.g., $C_1, C_2, c_0, c'$, are used to represent generic large and small constants, respectively. The actual values of these symbols for constants may vary across different lines.

To estimate $\beta^*$ in the log-error-in-variable model (5), one classic method is to perform simple normalization, i.e., to use $W_{ij}/N_i$ as a surrogate for $X_{ij}$ and implement the classic high-dimensional regularized estimators with $\log(W_{ij}/N_i)$ as covariates. As discussed in the introduction, this idea has two critical issues: first, the zero-valued $W_{ij}$’s need to be replaced by a small value to make them positive in the log transformation. The choice of this value is often difficult but critical to the performance of the final estimates; secondly, even though $\mathbb{E}(W_{ij}/N_i|N_i) = X_{ij}$, $\log(W_{ij}/N_i)$ may be a biased estimator for $\log(X_{ij})$, which can cause additional inaccuracy to the regression analysis. To further illustrate the biasness of $\log(W_{ij}/N_i)$ and to introduce our fixing plan, we first focus on the non-overdispersion case, i.e. when $W_i|N_i$ follows the regular multinomial distribution:

$$(W_{i1}, \ldots, W_{ip})|N_i \sim \text{Multinomial}(N_i, X_{i1}, \ldots, X_{ip}),$$

$$\mathbb{P}\{(W_{i1}, \ldots, W_{ip}) = (k_{i1}, \ldots, k_{ip})\} = \frac{N_i!}{k_{i1}! \cdots k_{ip}!} \prod_{j=1}^{p} X_{ij}^{k_{ij}},$$

where $k_{i1} + \cdots + k_{ip} = N_i$, $k_{i1}, \ldots, k_{ip} \in \{0, 1, 2, \ldots\}$. 

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In this case, we have \( W_{ij} \) following Poisson\((\nu_i X_{ij})\) and
\[
\mathbb{E}(W_{ij}) = \nu_i X_{ij}, \quad \text{var}(W_{ij}) = \nu_i X_{ij}(1 - X_{ij}) + \nu_i X_{ij}^2.
\]
For any \( z_i \geq 0 \), the Taylor expansion of \( \log(W_{ij} + z_i) \) at \( \nu_i X_{ij} \) yields the following approximation,
\[
\mathbb{E} \log(W_{ij} + z_i) \approx \log(\nu_i X_{ij}) + \frac{\mathbb{E}(W_{ij} - \nu_i X_{ij} + z_i)}{\nu_i X_{ij}} - \frac{\text{Var}(W_{ij}) + 2z_i \mathbb{E}(W_{ij} - \nu_i X_{ij}) + z_i^2}{2\nu_i^2 X_{ij}^2}.
\]
\[
= \log(\nu_i X_{ij}) + \frac{z_i - 1/2}{\nu_i X_{ij}} - \frac{z_i^2}{2\nu_i^2 X_{ij}^2}.
\]
Since \( N_i \) is the total number of reads in sample \( i \) and is generally large in practice (e.g., around \( 10^4 \) to \( 10^5 \) in our real data example), we can assume \( \nu_i = \mathbb{E}N_i \) to be large. Then,
\[
\mathbb{E} \log((W_{ij} + z_i)/N_i) - \log(X_{ij}) \approx \frac{z_i - 1/2}{\nu_i X_{ij}} - \frac{z_i^2}{2\nu_i^2 X_{ij}^2} + \log(\nu_i) - \mathbb{E} \log(N_i)
\]
\[
\approx \frac{z_i - 1/2}{\nu_i X_{ij}} - \frac{z_i^2}{2\nu_i^2 X_{ij}^2}.
\]
We can see the bias of \( \log((W_{ij} + z_i)/N_i) \) for estimating \( \log(X_{ij}) \) is approximately \(-1/2\nu_i X_{ij}\) and \(-1/8\nu_i^2 X_{ij}^2\) when \( z_i = 0 \) and \( z_i = 1/2 \), respectively. For large \( \nu_i \), one has \( 1/8\nu_i^2 X_{ij}^2 \ll (1/2)\nu_i X_{ij} \). Therefore, heuristically \( \log((W_{ij} + 1/2)/N_i) \) is a significantly less biased estimator for \( \log(X_{ij}) \) compared to \( \log(W_{ij}/N_i) \). Figure 1 illustrates the bias of \( \log(W \lor 0.5) \) (i.e., replacing zeros by \( 1/2 \)) and \( \log(W + c), c = 1/4, 1/2, 3/4, 1 \) for estimating \( \log(\nu) \) when \( W \) follows Poisson\((\nu)\). The plot suggests that \( \log(W + 1/2) \) achieves the minimum bias among these choices. In addition, by adding the positive value \( 1/2 \) to all \( W_{ij}s \), the earlier mentioned zero-replacement issue is simultaneously solved!

To account for higher variability in the count data, we also consider the overdispersed case where \( W_i|N_i \) satisfies Dirichlet-multinomial distribution [Mosimann 1962],
\[
(W_{i1}, \ldots, W_{ip})|N_i \sim \text{Dirichlet-Multinomial}(N_i, \alpha_i X_{i1}, \ldots, \alpha_i X_{ip}),
\]
\[
\mathbb{P}\left\{(W_{i1}, \ldots, W_{ip}) = (k_{i1}, \ldots, k_{ip}) \mid (N_i, q_{i1}, \ldots, q_{ip})\right\} = \frac{N_i!}{k_{i1}! \cdots k_{ip}!} \prod_{j=1}^{p} q_{ij}^{k_{ij}},
\]
\[
f(q_{i1}, \ldots, q_{ip}|N_i) = \frac{1}{B(\alpha_i X_{i1}, \ldots, \alpha_i X_{ip})} \prod_{j=1}^{p} q_{ij}^{\alpha_i X_{ij} - 1},
\]
where \( k_{i1} + \cdots + k_{ip} = N_i, k_{i1}, \ldots, k_{ip} \in \{0, 1, 2, \ldots\}, \quad q_{i1} + \cdots + q_{ip} = 1, q_{i1}, \ldots, q_{ip} \geq 0, \)
Here, $W \sim \text{Poisson}(\nu)$. Here, $B(\alpha_i X_{i1}, \ldots, \alpha_i X_{ip}) = \prod_{j=1}^{p} \frac{\Gamma(\alpha_i X_{ij})}{\Gamma(\alpha_i)}$ is the Beta function and $\alpha_i$ represents the level of overdispersion. When $\alpha_i < \infty$, we have

$$E(W_{ij}) = \nu_i X_{ij}, \quad \text{var}(W_{ij}) = \frac{\nu_i + \alpha_i + 1}{\alpha_i + 1} \cdot \nu_i X_{ij}(1 - X_{ij}) + \nu_i X_{ij}^2.$$  

Similarly, by investigating the Taylor expansion of $E(\log((W_{ij} + z_i)/N_i))$, it can be shown that taking $z_i = \frac{N_i + \alpha_i + 1}{2(\alpha_i + 1)}$ will make $\log((W_{ij} + z_i)/N_i)$ a better estimator for $\log(X_{ij})$ (more rigorous argument is postponed to the proof of Lemma 5 in the supplementary materials). It is noteworthy that $z_i$ is an estimate for half of $\frac{\nu_i + \alpha_i + 1}{\alpha_i + 1}$, which quantifies the overdispersion rate of $W_{ij}$ compared with the multinomial distribution.

These heuristic arguments inspire us to the following variable correction regularized estimator for the log-error-in-variable regression in (4) and (5):

$$\hat{\beta} = \arg \min_{\beta} \left( \frac{1}{2n} \|y - B_W \beta\|_2^2 + \lambda \|\beta\|_1 \right) \quad \text{subject to} \quad \sum_{j=1}^{p} \beta_j = 0,$$

where $B_W \in \mathbb{R}^{n \times p}$ and $(B_W)_{ij} = \log \left( W_{ij} + \frac{N_i + \alpha_i + 1}{2(\alpha_i + 1)} \right)$.
Particularly if $\alpha_i = \infty$, i.e., $W_i|N_i$ satisfies multinomial without overdispersion, $(B_W)_{ij} = \log(W_{ij} + 1/2)$.

**Remark 1** (Interpretation of Variable Correction). Different from the classic zero-replacement scheme that replaces only the zero covariates by a fixed value, we propose to add $1/2$ to all covariates in the non-overdispersion case. For overdispersed sample, say $W_i$, we propose to correct with a larger value: $z_i = \frac{N_i + \alpha_i + 1}{2(\alpha_i + 1)}$. In particular, with smaller total count $N_i$ or larger degree of overdispersion (i.e., smaller $\alpha_i$), the observable count covariates $W_i$ contains much noisier information about the true underlying composition $X_i$. Thus, we add larger values to alleviate the effect of overly large or small counts due to overdispersion.

**Remark 2.** When there are multiple samples $W_i$ that share the same $X_i$ and $\alpha_i$ and when there is evidence of overdispersion in practice, $\alpha_i$ can be estimated by method of moment estimator (La Rosa et al., 2012; Mosimann, 1962; Tvedebrink, 2010; Weir and Hill, 2002) or maximum likelihood estimator (Tvedebrink, 2010). Otherwise, $\alpha_i = +\infty$ and $z_i = 1/2$ are suggested. The more detailed discussions on the method of moment estimator of $\alpha_i$ is given in Section A of the supplementary materials.

### 3 Theoretical Analysis

In this section, we investigate the theoretical performance of the proposed variable correction regularized estimator for the log-error-in-variable regression model. We first focus on the case of $(W_1, \ldots, W_m)|N_i$ following multinomial distribution without overdispersion.

For convenience, denote $\bar{\nu} = \sum_{i=1}^n \nu_i/n$ and $\nu = (\nu_1, \ldots, \nu_n)^\top$. We say a matrix $M \in \mathbb{R}^{n \times p}$ satisfies the restricted isometry property (RIP) (Candes and Tao, 2005; Candes et al., 2007) with constant $\delta_s(M) \in (0, 1)$ if for all $s$-sparse vector $\beta \in \mathbb{R}^p$,

$$n(1 - \delta_s(M))\|\beta\|_2^2 \leq \|M\beta\|_2^2 \leq n(1 + \delta_s(M))\|\beta\|_2^2. \quad (8)$$

The RIP condition has become one of the most commonly used regularity condition in high-dimensional regression literature since its introduction. Denote $B_W \in \mathbb{R}^{n \times p}$ with $(B_W)_{ij} = \log \left(W_{ij} + \frac{N_i + \alpha_i + 1}{2(\alpha_i + 1)}\right)$ as the corrected design matrix. We assume the centralized and corrected design matrix $\bar{B}_W = B_W(I_p - \frac{1}{p}1_p1_p^\top)$ satisfies the RIP condition with high probability.
Condition 1 (RIP Condition). $\tilde{B}_W$ satisfies RIP condition with constant $\delta_{2s}(\tilde{B}_W) < 1/10$ with probability $1 - \epsilon'$ for some small quantity $\epsilon'$.

Remark 3. Denote $V, \tilde{V} \in \mathbb{R}^{n \times p}$ where $(V)_{ij} = \log(\nu_i X_{ij})$ and $\tilde{V} = V(I_p - \frac{1}{p}1_p1_p^\top)$. Lemma 14 in the supplementary materials shows that Condition 1 holds if the deterministic matrix $\tilde{V}$ satisfies RIP condition with constant $\delta_{2s}(\tilde{V}) < 1/20$ in the case without overdispersion.

The following sample complexity condition matches the classic results in high-dimensional regression (see, e.g., Candes et al. (2007); Bickel et al. (2009)).

Condition 2 (Sample Complexity). Assume a sufficient number of observations can be observed: $n \geq Cs \log p$ for some large constant $C$.

Based on these conditions, we show the proposed variable correction regularized estimator satisfies the following upper bound with high probability.

Theorem 1 (Upper Bound). Consider the log-error-in-variable regression model (4) and (5), where $\alpha_i = \infty$, i.e. $W$ has no overdispersion. Suppose Conditions 1 and 2 hold, and $a \bar{\nu} \leq \nu_i \leq b \bar{\nu}$, $a/p \leq X_{ij} \leq b/p$ for constants $0 < a < 1 < b$. If for some large constant $C > 0$, some $\epsilon > 0$, and a constant $C_\epsilon$ that only depends on $\epsilon$, we have $\bar{\nu} \geq \max\{p \cdot (sn)^{1/2 + \epsilon}, Cp \log(np), C_\epsilon/n\}$, then by choosing $\lambda = C \sqrt{\frac{\log p}{n}} \left(\sigma^2 + \frac{P}{\bar{\nu}} \|\beta^*\|_2^2\right)$ for some large constant $C > 0$, the variable correction regularized estimator (7) satisfies

$$
\|\hat{\beta} - \beta^*\|_2^2 \leq \frac{Cs \log p}{n} \left(\sigma^2 + \frac{P}{\bar{\nu}} \|\beta^*\|_2^2\right)
$$

with probability at least $1 - 4p^{-C'} - \epsilon'$.

Remark 4. Theorem 1 shows that the estimation error upper bound decreases with larger sample size $n$, smaller dimension $p$, smaller noise variance $\sigma^2$, higher average expectation of count $\bar{\nu}$, smaller signal amplitude $\|\beta^*\|_2^2$, or smaller sparsity level $s$.

Remark 5. We briefly discuss the sketch of the highly non-trivial proof for Theorem 1 here. First, we develop a series of inequalities on the corrected covariates in Lemmas 1-3 based on the tail probability bounds of Poisson, multinomial, and sub-Gaussian distributions. Then we develop an upper bound for $\|\tilde{B}_W (\tilde{B}_W \beta^* - y)\|_\infty$, a pivotal term in high-dimensional
regression analysis, in Lemma 4. Finally, we combine these inequalities with Condition 1 and obtain the upper bound for estimation error. The biggest challenge in the proof is to bound the corrected covariates \( \log(W_{ij} + \frac{1}{2}) \). Although the aforementioned Taylor’s expansion heuristically show \( \log(W_{ij} + \frac{1}{2}) \) are good estimators for \( \log(\nu_{ij}) \), more careful analysis is needed to obtain rigorous upper bounds on their biases and variances. To this end, we perform truncation on \( W_{ij} \) as the direct application of Poisson tail bounds may not yield sharp enough results.

**Remark 6.** We introduce the entry-wise upper and lower bounds of \( \nu_i \) and \( X_{ij} \) in Theorem 1 mainly to regularize the tail probability of \( W_{ij} \) that enables us to derive the minimax-optimal error bounds for the proposed procedure. Actually, similar conditions appeared in a range of literature on Poisson and multinomial inverse problems, e.g., Poisson matrix completion (Cao and Xie 2016, Equation (10)), Poisson sparse regression (Jiang et al. 2015, Assumption 2.1), composition matrix estimation from sparse count data (Cao et al. 2017, Remark 3), and Point autoregressive model (Hall et al. 2016, Definition of \( A_s \)) among many others. Such assumptions are mainly for technical purposes and may not be as crucial in practice as illustrated by the forthcoming real data and simulation studies.

To derive the lower bound for estimation error, we consider the following class of covariate matrices and parameter vectors,

\[
F_{p,n,s}(R, Q) = \left\{ (\nu, X, \beta) : a\nu \leq \nu_i \leq b\nu, a/p \leq X_{ij} \leq b/p \text{ for constants } 0 < a < 1 < b; \right.
\]

\[
\text{V satisfies RIP conditon with } \delta_{2s}(\text{V}) < \frac{1}{20};
\]

\[
|||\beta|||_2 \leq R, 1^\top_p \beta = 0, e^{-\frac{3}{2}}Q \leq \nu \leq e^{\frac{3}{2}}Q \right\}.
\] (10)

The constraints in \( F_{p,n,s}(R, Q) \) correspond to the regularization assumptions in Theorem 1.

The upper bound in Theorem 1 turns out to match the minimax lower bound in \( F_{p,n,s}(R, Q) \).

**Theorem 2** (Lower Bound). Suppose \( \varepsilon_i \overset{iid}{\sim} N(0, \sigma^2) \). If we have \( n \geq Cs \log p \) for some large constant \( C > 0 \), \( R \geq \bar{c} \sqrt{\frac{s \log(p/s)}{n}} \sigma^2 \) for some constant \( \bar{c} > 0 \), \( Q \geq p \), and \( s \geq 4 \), then

\[
\inf_{\hat{\beta}} \sup_{(\nu, X, \beta) \in F_{p,n,s}(R, Q)} \mathbb{E} \left\| \hat{\beta} - \beta \right\|_2^2 \geq \frac{cs \log(p/s)}{n} \left( \sigma^2 + \frac{p}{Q} R^2 \right)^2.
\] (11)
Remark 7. The lower bound in Theorem 2 consists of two terms: \( \frac{c_s \log(p/s)}{n} \sigma^2 \) and \( \frac{c_s \log(p/s)}{n} \cdot \frac{p}{Q} R^2 \), which originate from the uncertainty of \( \varepsilon \) and \( W \), respectively. We thus show \( \inf \sup E \| \hat{\beta} - \beta \|_2^2 \geq \frac{c_s \log(p/s)}{n} \sigma^2 \) and \( \inf \sup E \| \hat{\beta} - \beta \|_2^2 \geq \frac{c_s \log(p/s)}{n} \cdot \frac{p}{Q} R^2 \) separately in the proof of this theorem. While the first inequality develops from the classic high-dimensional regression literature (see, e.g., Rigollet and Tsybakov (2011)), the proof for the second one is far more complicated. In particular, we construct a series of instances of \( (\nu(i), X(i), \beta(i))_{i=1}^N \) satisfying the constraints in (10) and \( \text{diag}(\nu(i)) X(i) \beta(i) = \text{diag}(\nu(j)) X(j) \beta(j) \) for all \( i, j \). By such the design, \( y(i) = \text{diag}(\nu(i)) V(i) \beta(i) + \varepsilon(i) \) becomes “nullified” for estimating \( \beta(i) \) and we show these instances are non-distinguishable based a sample of \( (W(i), y(i)) \). Then we apply the generalized Fano’s lemma and establish the desired error lower bound.

Remark 8. Theorems 1 and 2 together show that the proposed procedure (7) achieves the optimal rate of convergence in \( \mathcal{F}_{p,n,s}(R) \) as long as \( \log(p/s) \) and \( \log(ep/s) \) are in the same order.

Next, we further consider the overdispersed case where \( \alpha_i < \infty \) in Model (4) and (5). We have the following upper bound for estimation accuracy of the proposed variable correction regularized estimator (7) with covariates \( B_W : (B_W)_{ij} = \log \left( W_{ij} + \frac{N_i + \alpha_i + 1}{2} \right) \).

Theorem 3 (Upper Bound for Overdispersed Log-Error-in-Variable Regression). Suppose Conditions 1 and 2 hold, and \( a \bar{\nu} \leq \nu_i \leq b \bar{\nu} \), \( a/p \leq X_{ij} \leq b/p \) for constants \( 0 < a < 1 < b \). Set \( \zeta_{\max} = \max_i \zeta_i \), where \( \zeta_i = \frac{\nu_i + \alpha_{i+1}}{2(\alpha_i + 1)} \) represents the level of overdispersion for \( i \)th sample. If for some \( \delta > 0 \), some large constant \( C \), and a large constant \( C(\delta) \) that only depends on \( \delta \), we have

\[
\nu_{ij} \geq \zeta_{i+1}^{1+\delta}, \quad \frac{\bar{\nu}}{\zeta_{\max}} \geq p \cdot \max \left\{ C \log(np), \frac{4n}{\log p} \left( \frac{1+\delta}{\delta} \right)^2 \log^2 \left( \frac{n}{\log p} \left( \frac{1+\delta}{\delta} \right)^2 \right), C(\delta) \right\},
\]

and \( n \geq C s \log p \), then by choosing \( \lambda = C \sqrt{\frac{\log p}{n}} \left( \sigma + \frac{p \zeta_{\max}}{\bar{\nu}} \| \beta^* \|_1 \right) \), we have

\[
\| \hat{\beta} - \beta \|_2^2 \leq \frac{C s \log p}{n} \left( \sigma^2 + \frac{p}{\bar{\nu}} \zeta_{\max} \cdot \| \beta^* \|_1 \right)
\]

with probability \( 1 - 6p^{-C'} - \epsilon' \), where \( C' \) is a large constant.
4 General High-dimensional Log-Error-in-Variable Regression

In this section, we further extend the discussion to general high-dimensional log-error-in-variable regression that accommodates broader scenarios. Specifically, let

\[ y = V \beta^* + \varepsilon, \quad \text{or equivalently} \quad y_i = \sum_{j=1}^{p} \log(\nu_{ij}) \beta_j^* + \varepsilon_i \quad \text{subject to} \quad C^T \beta^* = 0, \]  

(13)

where \( V = (\log(\nu_{ij}))_{1 \leq i \leq n, 1 \leq j \leq p} \) are unknown underlying covariates, \( \mathbb{P}_{\nu} \) is some general class of distributions with mean parameter \( \nu \), \( \varepsilon_i \) are i.i.d. sub-Gaussian noises with mean zero and variance \( \sigma^2 \), \( \beta^* \) is the sparse parameter of interest, and \( C \) is a \( p \times r \) matrix with each column representing a linear constraint on the regression coefficients. We aim to estimate \( \beta^* \) based on \( y \) and \( W \).

Assume that \( W \sim \mathbb{P}_{\nu} \). Suppose one can find a good estimate for \( \log(\nu) \), say \( \phi(W) \). Based on previous discussions, one can choose \( \phi(W) = \log \left( W + \frac{1}{2} \right) \) if \( \mathbb{P}_{\nu} \) is Poisson distribution with parameter \( \nu \). Some other choices include: \( \phi(\nu) = \log \left( (\nu + \frac{1}{2}) \vee 1 \right) \) if \( \mathbb{P}_{\nu} \sim N(\nu, \gamma \nu) \); \( \phi(\nu) = \log(\nu + \gamma/2) \) if \( \mathbb{P}_{\nu} \sim \text{Gamma}(\nu, \gamma) \) (i.e., Gamma distribution with shape parameter \( \nu \), scale parameter \( \gamma \), and pdf \( f(x) = \frac{1}{\Gamma(\nu)\gamma^{\nu}} x^{\nu-1} e^{-x/\gamma} \)).

Similarly to Section 2, we propose the following variable correction regularized estimator for \( \beta^* \) in general high-dimensional log-error-in-variable regression model (13),

\[ \hat{\beta} = \arg \min_{\beta} \left( \frac{1}{2n} \| y - B_W \beta \|_2^2 + \lambda \| \beta \|_1 \right) \quad \text{subject to} \quad C^T \beta = 0. \]  

(14)

Here, \( B_W \in \mathbb{R}^{n \times p} \) with \( (B_W)_{ij} = \phi(W_{ij}) \) and \( \lambda \) is some tuning parameter. Define \( P_C = C(C^T C)^{\dagger} C^T \) as the projection matrix onto the column space of \( C \) where \( (\cdot)^\dagger \) represents matrix pseudoinverse. We introduce the following regularity conditions for the theoretical analysis of the proposed estimator.

**Condition 3.** \( \| I_p - P_C \|_\infty \leq k_0 \) for a constant \( k_0 \) that is free of \( p \). Also, \( 1_p \) belongs to the column space of \( C \), i.e., \( (I_p - P_C) 1_p = 0 \).
Condition 4. $\tilde{B}_W = B_W(I_p - P_C)$ satisfies RIP condition (8) with $\delta_{2s}(\tilde{B}_W) < 1/10$ with probability at least $1 - \epsilon'$ for some small quantity $\epsilon$.

Conditions 3 and 4 are regularization assumptions for the constraint and covariates, respectively. The requirement of $(I_p - P_C)1_p = 0$ in Condition 3 can be omitted if we include an intercept in the regression equation. Condition 4 can be seen as a parallel version of Condition 1 in the previous section.

Condition 5. Suppose $W \sim P_\nu$. There exists a non-negative increasing function $\pi(x)$ such that

1. there exist a constant $K_0$ such that $\left\| \sqrt{\pi(\nu)} (\phi(W_{ij}) - E\phi(W_{ij})) \right\|_2 \leq K_0$, where $\|X\|_2 = \sup_{p \geq 1} p^{-1/2}(E|X|^p)^{1/p}$ is the Orlicz norm of random variables;

2. $\frac{\pi(tx)}{\pi(x)} \leq C_t$ with $C_t$ only depending on $t \geq 1$;

3. $\lim_{x \to \infty} \pi(x) = \infty$;

4. $\max \{|\log \phi^2(W) - \log^2 \nu|, (\log \nu |\log \phi(W) - \log \nu|)\} = o\left(1/\sqrt{\pi(\nu)} \right)$ as $\nu \to \infty$.

Condition 5 is introduced to regularize the tail property of distribution $P_\nu$ and the $\pi(\cdot)$ function essentially characterizes the accuracy of estimator $\phi(W)$ to $\log(\nu)$. In particular, if $P_\nu$ are Poisson($\nu$), Gamma($\nu, \gamma$), or $N(\nu, \gamma \nu)$, $\pi(t) = t$ satisfies Condition 5.

The following theorem provides an upper bound for the variable correction regularized estimator in the general high-dimensional log-error-in-variable regression model.

**Theorem 4 (General Upper Bound).** Suppose Conditions 2, 3, 4, and 5 hold, and in addition $|\log \nu_{ij} - \log \nu_{kl}| \leq a$ for some constant $a > 0$ for all $1 \leq i, k \leq n, 1 \leq j, l \leq p$. Denote $\bar{\nu} = \frac{1}{n} \sum_{i=1}^{n} \sum_{j=1}^{p} \nu_{ij}$. If for some uniform constant $C > 0$ and constant $C_{n,s}$ that only depends on $s$ and $n$, we have $\bar{\nu} > pC_{n,s}$, then by choosing $\lambda = C \sqrt{\frac{\log p}{n} \left(\sigma^2 + \frac{1}{\pi(\nu/p)} \|\beta^*\|_2^2\right)}$, we have

$$\|\hat{\beta} - \beta^*\|_2^2 \leq \frac{Cs \log p}{n} \left(\sigma^2 + \frac{1}{\pi(\bar{\nu}/p)} \|\beta^*\|_2^2\right)$$

with probability $1 - 3p^{-C'} - \epsilon$.

The following lower bound result suggests the optimality of the proposed estimator.
Theorem 5 (General Lower Bound). Suppose \( \varepsilon_i \overset{\text{i.i.d.}}{\sim} N(0, \sigma^2) \). Assume \( \varphi(x) \) is an increasing function with \( \varphi(1) \geq 1 \) and the Kullback-Leibler divergence between \( P_{\nu_1} \) and \( P_{\nu_2} \) satisfies \( D_{KL}(P_{\nu_1}, P_{\nu_2}) \leq C \varphi(\nu_1) \left( \log(\nu_1) - \log(\nu_2) \right)^2 \) for all \( \nu_1 \) and \( \nu_2 \) satisfying \( |\log(\nu_1) - \log(\nu_2)| \leq 1 \). If \( n \geq Cs \log p \) for some large constant \( C > 0 \), \( R \geq \bar{c} \sqrt{\frac{s \log(\frac{p}{s})}{n}} \sigma^2 \) for some constant \( \bar{c} > 0 \) and \( Q \geq p, s \geq 4 \), then we have

\[
\inf_{\beta} \sup_{(V, C, \beta) \in \mathcal{F}_{p,n,s}(R,Q)} \mathbb{E} \left\| \hat{\beta} - \beta \right\|^2 \geq \frac{cs \log(p/s)}{n} \left( \sigma^2 + \frac{1}{\varphi(CQ/p)} R^2 \right),
\]

where

\[
\mathcal{F}_{p,n,s}(R,Q) = \left\{ (V, C, \beta) : C \text{ satisfies Conditions } \| \beta \|_2 \leq R, C^\top \beta = 0, |\log \nu_{ij} - \log \nu_{kl}| \leq a \text{ for constant } a > 0 \text{ for all } 1 \leq i, k \leq n, 1 \leq j, l \leq p, \bar{V} \text{ satisfies RIP condition with } \delta_{2s}(\bar{V}) < \frac{1}{20}, e^{-\frac{3}{2}} Q \leq \bar{\nu} \leq e^{\frac{3}{2}} Q \right\}.
\]

By comparing the upper and lower bounds in Theorems 4 and 5, we can see the proposed method achieves optimal rates when \( \phi(\cdot) \) and \( \pi(\cdot) \) are of the same order, which can be guaranteed when \( P_{\nu_*} \) is a distribution class with good properties, e.g., the aforementioned Normal(\( \nu, \gamma \)), Gamma(\( \nu, \gamma \)), or Poisson(\( \nu \)).

5 Numerical Studies

5.1 Regression Analysis for Longitudinal Microbiome Studies

In this section, we apply the proposed procedure to a longitudinal microbiome study reported by [Flores et al. (2014)]. In this study, 3655 microbiome samples were taken repeatedly from gut (feces) and several other body sites of 85 college-age adults in a range of three months. Other clinical covariates including body mass index (BMI), antibiotic disturbance and medication use were also documented. The microbiome samples were then processed using 16S ribosomal RNA sequencing, characterized into Operational Taxonomic Units (OTUs) using
the QIIME pipeline, and combined into taxonomic groups at different taxonomic levels from phyla to species.

We focus on the association between BMI and gut microbiome composition at the genus level for healthy adults by excluding subjects that have missing BMI, antibiotic disturbance, or other medication use. For the 352 samples from the remaining 40 subjects, 92 bacteria genera appear in more than 10% of the samples and will be used for the analysis forward. For each subject, we include four samples that are most similar to each other based on Bray-Curtis distance. We consider these 4 samples to be more representative of their owners’ true gut microbiome composition since the samples of some subjects varies significantly across time due to possibility of sample contamination or other unobserved factors. As a result, we have 160 samples from 40 subjects, each subject with 4 samples, and 92 bacteria genera for the regression analysis.

We implement the proposed variable correction regularized estimator (VC) based on the high-dimensional log-error-in-variable regression model. Specifically, we assume the four samples of the same subject to share the same unobserved composition $X_{ij}$ and overdispersion parameter $\alpha_i$ and estimate $\alpha_i$ for each subject respectively using the method of moment estimator $\hat{\alpha}_{i,MOM}$ described in Section A in the supplementary materials. Then we apply the regression model (18) with $y$ representing BMI, $W_{ij}$ representing read count of the $i$th sample and $j$th genus:

$$
\hat{\beta} = \arg\min_{\beta:1_p, \beta = 0} \left\{ \frac{1}{2n} \sum_{i=1}^{n} \left( y_i - \sum_{j=1}^{p} \log (W_{ij} + z_i) \beta_j \right)^2 + \lambda ||\beta||_1 \right\},
$$

(18)

where $z_i = \frac{N_i + \hat{\alpha}_{i,MOM} + 1}{2(\hat{\alpha}_{i,MOM} + 1)}$.

(19)

For comparison, we also perform the classic zero-replacement method (ZR) in literature with zero counts changed to $c = 0.1$ and 0.5, respectively:

$$
\hat{\beta}^{\text{Zr}} = \arg\min_{\beta:1_p, \beta = 0} \left\{ \frac{1}{2n} \sum_{i=1}^{n} \left( y_i - \sum_{j=1}^{p} \log (W_{ij} \lor c) \beta_j \right)^2 + \lambda ||\beta||_1 \right\}.
$$

(20)

To obtain stable variable selection, we generate 100 bootstrap samples of size $n/2$, repeat all methods with five-fold cross-validation choosing the tuning parameter $\lambda$ on each subsample,
and record the frequency of each variable being selected among the 100 bootstrap fittings. We consider a variable to be selected if its selection frequency is no less than 0.6.

Figure 2 illustrates the selection frequency of 92 genera for each method. The dashed line corresponds to the selection frequency of 0.6. It can be observed that the variable correction regularized estimator (VC) selects variables with either very high or very low frequency, while zero-replacement estimator (ZR) has much more variables selected with a mid-range frequency. This comparison indicates that VC has much better stability in variable selection than ZR. The variables selected by variable correction are: Actinomyces(-), Akkermansia(-), Bacteroides(-), Coprococcus(+), Desulfovibrio(-), Dialister(+), Haemophilus(+), Megamonas(+), Porphyromonas(-), Prevotella(+), Sutterella(+), Veillonella(-), where (+) and (-) are signs of the fitted regression coefficients. The variables selected by ZR with \(c = 0.5\) are: Arcanobacterium(-), Bacteroides(-), Dialister(+), Haemophilus(+), Prevotella(+), Slackia(+). Here, “(+)” and “(-)” represent positive and negative effects, respectively. No variable is selected by zero-replacement with \(c = 0.1\). These selected genera correspond to the bars exceeding the dashed line in the left panel (VC) and middle panel (ZR with \(c = 0.5\)) of Figure 2 from left to right. Among the genera selected by VC but missed by ZR with \(c = 0.5\), Akkermansia has been reported to be negatively related with obesity in extensive literature (Dao et al., 2015; Derrien et al., 2017; Karlsson et al., 2012; Zhang et al., 2009) and type II diabetes (Qin et al., 2012). Coprococcus has also been broadly reported to be positively related with obesity (Kasai et al., 2015) and negatively related with weight loss induced by diet or gastric bypass surgery, as indicated by Damms-Machado et al. (2015); Di Luccia et al. (2015); Graessler et al. (2013).

Figure 3 offers a closer look at the selection frequency with regard to the proportion of \(W_{ij} = 0\) for each variable. Compared to ZR, the proposed VC has more preference towards variables with fewer zeros, although the preference is not decisive. This contrast of behavior between CV and ZR makes VC more desirable since the bacteria with large proportions of zeros are often far less reliable for prediction and interpretation purposes since they are possessed by only a few subjects and are more difficult to generalize to a larger population. Figure 4 compares the prediction performance of VC and ZR with \(c = 0.5\), where the
predicted BMI for each sample is obtained using refitted coefficients of the genera that have selection frequency no less than 0.6. Since each subject has four samples, we also provide the averaged predicted BMI of each subject in Figure 4. The $R^2$ in Figure 4 is computed using the individual sample points. The $R^2$ using averaged predicted BMI is 0.63 for VC and 0.49 for ZR with $c = 0.5$. Here, the proposed VC achieves much better prediction compared with ZR using both individual predicted BMI and average predicted BMI.

5.2 Simulation Studies

Next, we evaluate the numerical performance of the proposed procedure on synthetic datasets. To simulate the count matrix $W$ with $n$ samples and $p$ covariates, we first generate $N_i$ from negative binomial distribution with mean $3 \times 10^4$ and variance $3 \times 10^6$. Here, the main purpose of choosing negative binomial instead of the Poisson in previous theoretical analysis is to show that the Poisson assumption on $N_i$ is not crucial in real practice. Then we set $X_{ij} = X_{i+n/2,j} = \frac{\exp(\Phi_{ij})}{\sum_{k=1}^p \exp(\Phi_{ik})}$ for $j = 1, \ldots, p, i = 1, \ldots, n/2$ with $\Phi_{ij}$s generated independently from $N(\mu_j, 1.5^2)$, where $\mu_1, \ldots, \mu_3$ are drawn from Uniform[1,3], $\mu_4, \ldots, \mu_7$ are drawn from Uniform[2,4], and $\mu_j$ for $j = 8, \ldots, p$ are drawn from Uniform[0,2]. With this setting, the average count of covariates will have a reasonable vari-
Figure 3: Comparison of selection frequency with regard to proportion of zero counts

Figure 4: Comparison of prediction performance
We generate $W_{ij}$ from Dirichlet-Multinomial($N_i, \alpha X_{i1}, \ldots, \alpha X_{ip}$), where the overdispersion parameter $\alpha = 200, 1000, 5000$. The $i$th and $(i + n/2)$th samples are designed to be from the same subject so they share the same $X_{ij}$ and can be used to estimate their shared overdispersion parameter. The response $y$ is generated as $y_i = \sum_{j=1}^{p} \log(X_{ij}) \beta_j + \varepsilon_i$, where $\beta = (1, -0.8, -1.5, 0.6, -0.9, 1.2, 0.4, 0, \ldots, 0)$ is the deterministic coefficient vector and $\varepsilon_i$ are i.i.d. noise generated from $N(0, 0.5^2)$. We perform simulation study with $n = 50, 100$ and $p = 100, 200, 400$.

Using the simulated data, we evaluate the performance of the proposed variable correction regularized estimator (VC) and the classic zero-replacement with $c = 0.5$ (ZR0.5) in estimation and prediction errors. The results are aggregated in Figure 5. We can see VC significantly outperforms ZR0.5 in all parameter configurations.

To evaluate the performance of the proposed method when the response variable $y$ is shared by samples from the same subject like what we have in the real data analysis, we repeat the aforementioned simulation with one change: $y$ is generated with $\varepsilon_i = \varepsilon_{i+n/2}$ and $\varepsilon_i, i = 1, \ldots, n/2$ are i.i.d. from $N(0, 0.5^2)$. The results are summarized in Figure 6. We can see the pattern of performance is similar to that of Figure 5 and VC still significantly achieves smaller estimation and prediction errors.

6 Discussions

Understanding the association between microbial taxa and phenotypes is a crucial problem in microbiome study. To overcome the difficulties of randomness in covariates and zero-replacement in classic methods for compositional data regression, we introduce the novel log-error-in-variable regression model and the variable correction regularized estimator in this article. The proposed estimator is surprisingly simple, works on possible overdispersed data, and avoids any subjective zero replacement. When the count observations follow multinomial distribution without overdispersion, we propose to add a half to all counts, then performing the constrained Lasso estimator; when significant overdispersion exists, we
Figure 5: Comparison between variable correction regularized estimator (VC) and zero-replacement estimator with $c = 0.5$ (ZR0.5) in simulation analysis. Noises $\varepsilon_i$ are all independent.

Figure 6: Comparison between variable correction regularized estimator (VC) and zero-replacement estimator with $c = 0.5$ (ZR0.5) in simulation analysis. $y$ is shared by samples from the same subject.
propose to add a larger and reasonable value to all counts. We show that the proposed methods achieve minimax optimal performance in a general class of settings.

In addition to the aforementioned microbiome study, the proposed framework can be used to other applications on regression with count covariates. For example, in single-cell RNA-seq data analysis, the high-throughput sequencing technique was performed on each of the single cells and the gene expressions can be measured as the total number of reads mapped to exonic regions. This results count matrix with rows and columns representing single cells and gene expressions, respectively. With the proposed method, we can perform regression analysis to study the association among the gene expressions of single cells and clinical phenotypes. Another potential application is in text mining, where one central task of topic modeling is to learn the topics of various documents when they share the same vocabulary of words. By counting the number of words or n-grams for each document, one can obtain count matrix data. Compared to the absolute counts of these words and n-grams, the relative abundances may be more predictive on the topic. Thus, our proposed method is potentially useful for building classifiers for topics of documents.

7 Proofs

We collect the proofs of the main results in this section. For convenience, denote \( \nu_{\min} = \min_{k,i} \nu_{ki}, \nu_{\max} = \max_{k,i} \nu_{ki}, \phi_1 (W) = \log (W + \frac{1}{2}) , \phi_2 (W) = \log^2 (W + \frac{1}{2}) \) and

\[
A_W \in \mathbb{R}^{p \times p}, \quad A_W = B_W^T B_W, \quad P = I_p - \frac{1}{p} 1_p 1_p^T.
\]

In the log-error-in-variable regression case (Theorems 1, 2, and 3), denote

\[
\tilde{A}_W = PA_W P, \quad \tilde{B}_W = B_W P.
\]

In the general case (Theorems 4 and 5), denote

\[
\tilde{A}_W = (I_p - P_C) A_W (I_p - P_C), \quad \tilde{B}_W = B_W (I_p - P_C).
\]

We also denote the Orlicz-\( \psi_1 \) and \(-\psi_2\) norms as \( \|X\|_{\psi_1} = \sup_{p \geq 1} p^{-1}(\mathbb{E}|X|^p)^{1/p} \), \( \|X\|_{\psi_2} = \sup_{p \geq 1} p^{-1/2}(\mathbb{E}|X|^p)^{1/p} \) for any random variable \( X \).
7.1 Proof of Theorem 1

The model can be summarized as follows,

\[ y_i = \sum_{j=1}^{n} \log(X_{ij})\beta_j^* + \epsilon_i, \quad i = 1, \ldots, n; \quad (21) \]

\[ W_{ij} \sim \text{Poisson}(\nu_{ij}), \quad 1 \leq i \leq n; 1 \leq j \leq p. \quad (22) \]

Here \( y_i \) and \( W_{ij} \) are observable and \( \beta_i^*, \nu_{ij} = \nu_i X_{ij} \) are hidden parameters. The proposed estimator is as follows,

\[ \hat{\beta} = \arg \min_{\gamma} \left( \frac{1}{2n} \| y - B_W \gamma \|_2^2 + \lambda \| \gamma \|_1 \right) \quad \text{subject to} \quad \sum_{j=1}^{p} \gamma_j = 0. \quad (23) \]

In the following lemmas, suppose \( W \sim \text{Poisson}(v) \) and \( W' = W1\{v \leq W \leq 10v\} + v1\{W \notin [v, 10v]\} \):

**Lemma 1** (Bias of \( \log(W' + \frac{1}{2}) \)). For any \( \epsilon > 0 \), there exists \( C_\epsilon > 0 \) that only depends on \( \epsilon \), such that for all \( v \geq C_\epsilon \), we have \( |\mathbb{E} \log(W' + \frac{1}{2}) - \log v| \leq 4v^{-\frac{3}{2}} + \epsilon \).

**Lemma 2** (Bias of \( \log^2(W' + \frac{1}{2}) \)). There exists constant \( C > 0 \) such that if \( v \geq C \), then \( |\mathbb{E}(\log^2(W' + \frac{1}{2})) - \log^2 v| \leq \frac{4}{v} \).

**Lemma 3** (Sub-Gaussianity). There exist positive constants \( K_0 \) and \( C \), such that for \( v \geq C \), we have

\[ \left\| \sqrt{v} \left( \log(W' + \frac{1}{2}) - \mathbb{E} \log(W' + \frac{1}{2}) \right) \right\|_{\psi_2} \leq K_0. \]

**Lemma 4** (Infinity norm bound). Under the setting of Theorem 1, there exist two constants \( C \) and \( C' \) such that

\[ \mathbb{P} \left( \| A_W \beta^* - B_W^T y \|_\infty \leq C \sqrt{n \log p \left( \sigma^2 + \frac{p}{\nu} \| \beta^* \|_2^2 \right)} \right) \geq 1 - 4p^{-C'}. \]

Now let us move to the proof of Theorem 1. Denote \( h = \hat{\beta} - \beta^* \). By lemma 4, with probability at least \( 1 - 4p^{-C'} \),

\[ \| A_W \beta^* - B_W^T y \|_\infty \leq C \sqrt{n \log p \left( \sigma^2 + \frac{p}{\nu} \| \beta^* \|_2^2 \right)} = \frac{n}{2} \lambda. \quad (24) \]

By the definition of the estimator and the fact that \( P \beta^* = \beta^*, P \hat{\beta} = \hat{\beta} \), we have

\[ \frac{1}{2n} \| y - B_W \hat{\beta} \|_2^2 + \lambda \| \hat{\beta} \|_1 \leq \frac{1}{2n} \| y - B_W \beta^* \|_2^2 + \lambda \| \beta^* \|_1, \]

24
which means
\[
\frac{1}{2n} \left( 2h^\top (A_W \beta^* - B_W y) + h^\top A_W h \right) \leq \lambda \left( \|\beta^*\|_1 - \|\hat{\beta}\|_1 \right).
\]

Denote \( S = \text{supp}(\beta^*) \). Noting that
\[
\|\beta^*\|_1 - \|\hat{\beta}\|_1 = \|\beta^*\|_1 - \|\hat{\beta}\|_1 - \|\hat{\beta}\|_1 \leq \|\beta^* - \hat{\beta}\|_1 - \|h_{S^c}\|_1 \leq \|h_S\|_1 - \|h_{S^c}\|_1,
\]
we have
\[
\frac{1}{2n} \left( 2h^\top (A_W \beta^* - B_W y) + h^\top A_W h \right) \leq \lambda \left( \|h_S\|_1 - \|h_{S^c}\|_1 \right).
\]

In addition,
\[
\frac{1}{2n} \left( 2h^\top (A_W \beta^* - B_W y) + h^\top A_W h \right) = \frac{1}{2n} \left( 2h^\top (A_W \beta^* - B_W y) + \|B_W h\|^2 \right)
\]
\[
\geq \frac{1}{n} h^\top (A_W \beta^* - B_W y) \geq -\frac{1}{n} \|h\|_1 \|A_W \beta^* - B_W y\|_{\infty}
\]
\[
= -\frac{1}{n} (\|h_S\|_1 + \|h_{S^c}\|_1) \|A_W \beta^* - B_W y\|_{\infty}.
\]

If (24) holds, then (24), (25) and the previous inequality together imply
\[
-\frac{1}{2} (\|h_S\|_1 + \|h_{S^c}\|_1) \leq \|h_S\|_1 - \|h_{S^c}\|_1, \quad \text{i.e.,} \quad \|h_S\|_1 \geq \frac{1}{3} \|h_{S^c}\|_1.
\]

Therefore,
\[
\|h_{\max(s)}\|_1 \geq \|h_S\|_1 \geq \frac{1}{3} \|h_{S^c}\|_1 \geq \frac{1}{3} \|h_{\max(s)}\|_1,
\]
where we set \( h_{\max(s)} \) as \( h \) with all but the largest \( s \) entries in absolute value set to zero, and \( h_{\max(s)} = h - h_{\max(s)} \). By the KKT condition on (23), we have
\[
\left\| B_W^{-1} \left( B_W \hat{\beta} - y \right) + 1_p \kappa \right\|_{\infty} \leq n \lambda
\]
for some \( \kappa \in \mathbb{R} \). Since \( \|P x\|_{\infty} = \|x - \frac{1}{p} \sum_{i=1}^p x_i\|_{\infty} \leq \|x\|_{\infty} + \left| \frac{1}{p} \sum_{i=1}^p x_i \right| \leq 2 \|x\|_{\infty} \),
\[
\left\| A_W \hat{\beta} - B_W y \right\|_{\infty} = \left\| P \left( B_W^{-1} \left( B_W \hat{\beta} - y \right) + 1_p \kappa \right) \right\|_{\infty} \leq 2 \left\| B_W^{-1} \left( B_W \hat{\beta} - y \right) + 1_p \kappa \right\|_{\infty} \leq 2n \lambda.
\]

By (24) and the previous inequality, with probability at least \( 1 - 4p^{\gamma} \),
\[
\|A_W h\|_{\infty} = \left\| A_W \left( \beta^* - \hat{\beta} \right) \right\|_{\infty} \leq \|A_W \hat{\beta} - B_W y\|_{\infty} + \|A_W \beta^* - B_W y\|_{\infty} \leq \frac{5}{2} n \lambda.
\]

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Therefore, with probability at least $1 - 4p^{-C'}$,

$$h_{\text{max}(s)} A_W h \leq \|h_{\text{max}(s)}\|_1 \|A_W h\|_{\infty} \leq \frac{5}{2} n \lambda \cdot \sqrt{s} \|h_{\text{max}(s)}\|_2.$$  \hspace{1cm} (27)

Define $\alpha = \|h_{\text{max}(s)}\|_1 / s$, then

$$\|h_{-\text{max}(s)}\|_\infty \leq \alpha \leq 3\alpha, \quad \|h_{-\text{max}(s)}\|_1 \leq 3\|h_{\text{max}(s)}\|_1 = 3s\alpha.$$  

Apply Lemma 1.1 in Cai and Zhang (2014), $h_{-\text{max}(s)}$ can be expressed as a convex combinations of sparse vectors: $h_{-\text{max}(s)} = \sum_{i=1}^M \lambda_i u_i$, where $u_i$ is $s$-sparse and

$$\|u_i\|_1 = \|h^{(2)}\|_1, \quad \|u_i\|_\infty \leq 3\alpha, \quad \text{supp}(u_i) \subseteq \text{supp}(h_{-\text{max}(s)}).$$

Thus

$$\|u_i\|_2 \leq \sqrt{\|u_i\|_0} \|u_i\|_\infty \leq \sqrt{s} \cdot 3\alpha = 3\sqrt{s} \alpha.$$  \hspace{1cm} (28)

Suppose $0 \leq \mu \leq 1$ is to be determined. Denote $\gamma_i = h_{\text{max}(s)} + \mu u_i$, then

$$\sum_{j=1}^M \lambda_j \gamma_j - \frac{1}{2} \gamma_i = h_{\text{max}(s)} + \mu h_{-\text{max}(s)} - \frac{1}{2} \gamma_i = (1 - \mu - \frac{1}{2})h_{\text{max}(s)} - \frac{1}{2} \mu u_i + \mu h.$$  

Since $h_{\text{max}(s)}$ and $u_i$ are $s$-sparse vectors, $\gamma_i = h_{\text{max}(s)} + \mu u_i, \sum_{j=1}^M \lambda_j \gamma_j - \frac{1}{2} \gamma_i - \mu h = (\frac{1}{2} - \mu)h_{\text{max}(s)} - \frac{1}{2} \mu u_i$ are all $2s$-sparse vectors.

Suppose $x = \|h_{\text{max}(s)}\|_2$, by (28),

$$\|u_i\|_2 \leq 3\sqrt{s} \alpha \leq 3 \|h_{\text{max}(s)}\|_2 = 3x.$$  \hspace{1cm} (29)

Also, we can check that

$$\sum_{i=1}^M \lambda_i \left\|B_W \left( \sum_{j=1}^M \lambda_j \gamma_j - \frac{1}{2} \gamma_i \right) \right\|_2^2 = \sum_{i=1}^M \lambda_i \cdot \frac{1}{4} \|B_W \gamma_i\|_2^2.$$
\[0 = \sum_{i=1}^{M} \left\| \mathbf{B}_W \cdot \left( h_{\text{max}(s)} + \mu h_{\text{max}(s)} - \frac{1}{2} (h_{\text{max}(s)} + \mu u_i) \right) \right\|_2^2 - \sum_{i=1}^{M} \frac{\lambda_i}{4} \left\| \mathbf{B}_W \gamma_i \right\|_2^2\]

\[= \sum_{i=1}^{M} \left\| \mathbf{B}_W \left( \frac{1}{2} - \mu \right) h_{\text{max}(s)} - \frac{\mu}{2} u_i + \mu h \right\|_2^2 - \sum_{i=1}^{M} \frac{\lambda_i}{4} \left\| \mathbf{B}_W \gamma_i \right\|_2^2\]

\[= \sum_{i=1}^{M} \lambda_i \left\| \mathbf{B}_W \left( \frac{1}{2} - \mu \right) h_{\text{max}(s)} - \frac{\mu}{2} u_i \right\|_2^2 + 2\mu \left( \frac{1}{2} - \mu \right) h_{\text{max}(s)}^\top \mathbf{A}_W h\]

\[+ \mu^2 \left\| \mathbf{B}_W h \right\|_2^2 - \sum_{i=1}^{M} \frac{\lambda_i}{4} \left\| \mathbf{B}_W \gamma_i \right\|_2^2\]

\[= \sum_{i=1}^{M} \left\| \mathbf{B}_W \left( \frac{1}{2} - \mu \right) h_{\text{max}(s)} - \frac{\mu}{2} u_i \right\|_2^2 + \mu(1 - \mu) h_{\text{max}(s)}^\top \mathbf{A}_W h - \sum_{i=1}^{M} \frac{\lambda_i}{4} \left\| \mathbf{B}_W \gamma_i \right\|_2^2.\]

(30)

In the third equation above, we used the facts that \( h_{\text{max}(s)} = \sum_{i=1}^{M} \lambda_i u_i \) and \( \mathbf{A}_W = \mathbf{B}_W^\top \mathbf{B}_W \).

Noting that \( \text{supp}(h_{\text{max}(s)}) \cap \text{supp}(u_i) (i = 1, \ldots, M) \) are all empty sets and \( \gamma_i, (\frac{1}{2} - \mu) h_{\text{max}(s)} - \frac{\mu}{2} u_i \) are all \( 2s \)-sparse vectors, we can apply Condition 1 (27), and (29) to (30) and obtain

\[0 \leq n(1 + \delta_{2s}(\mathbf{B}_W)) \sum_{i=1}^{M} \lambda_i \left( \left( \frac{1}{2} - \mu \right)^2 \left\| h_{\text{max}(s)} \right\|_2^2 + \frac{\mu^2}{4} \left\| u_i \right\|_2^2 \right) + \frac{5}{2} n\mu(1 - \mu) \sqrt{s} \lambda \left\| h_{\text{max}(s)} \right\|_2\]

\[\leq n \sum_{i=1}^{M} \lambda_i \left\{ \left( (1 + \delta_{2s}(\mathbf{B}_W))(\frac{1}{2} - \mu)^2 - (1 - \delta_{2s}(\mathbf{B}_W)) \cdot \frac{1}{4} \right) \left\| h_{\text{max}(s)} \right\|_2^2 + \frac{1}{2} \delta_{2s}(\mathbf{B}_W) \mu^2 \left\| u_i \right\|_2^2 \right\}\]

\[+ \frac{5}{2} n\mu(1 - \mu) \sqrt{s} \lambda \left\| h_{\text{max}(s)} \right\|_2\]

\[\leq n \sum_{i=1}^{M} \lambda_i \left\{ \left( (1 + \delta_{2s}(\mathbf{B}_W))(\frac{1}{2} - \mu)^2 - (1 - \delta_{2s}(\mathbf{B}_W)) \cdot \frac{1}{4} \right) x^2 + \frac{1}{2} \delta_{2s}(\mathbf{B}_W) \mu^2 \cdot 9x^2 \right\}\]

\[+ \frac{5}{2} n\mu(1 - \mu) \sqrt{s} \lambda x\]

\[\leq n \left[ \mu^2 - \mu - \frac{1}{2} \delta_{2s}(\mathbf{B}_W) (1 - 2\mu + 11\mu^2) \right] x^2 + \frac{5}{2} n\mu(1 - \mu) \sqrt{s} \lambda x\]

holds with probability at least \( 1 - 4p^{-C'} - \epsilon' \). Set \( \mu = \frac{1}{2} \) and notice that \( \delta_{2s}(\mathbf{B}_W) \leq \frac{1}{10} \), we know that with probability at least \( 1 - 4p^{-C'} - \epsilon' \),

\[x \leq \left( 1 - \frac{11}{2} \delta_{2s}(\mathbf{B}_W) \right)^{-1} \frac{5}{2} \sqrt{s} \lambda \leq \frac{50}{9} \sqrt{s} \lambda.\]
Therefore, with probability at least $1 - 4p^{-C'} - \epsilon'$,

$$\|h\|_2 = \sqrt{\|h_{\max(s)}\|_2^2 + \|h_{-\max(s)}\|_2^2} \leq \sqrt{\|h_{\max(s)}\|_2^2 + 9\|h_{\max(s)}\|_2^2} = \sqrt{10}x \leq 18\sqrt{s}\lambda,$$

which means with probability at least $1 - 4p^{-C'} - \epsilon'$,

$$\|\hat{\beta} - \beta^*\|_2^2 \leq 324s\lambda^2 = C_s\frac{\log p}{n} \left( \sigma^2 + \frac{p}{b}\|\beta^*\|_2^2 \right).$$

\[\square\]

### 7.2 Proof of Theorem 3

$W_{ij}$ can be seen as $W_{ij}|q_i \sim \text{Poisson}(\nu_i q_{ij})$ and $q_{ij} \sim \text{Beta}(\alpha_i X_{ij}, \alpha_i - \alpha_i X_{ij})$. We introduce the truncated version of $W_{ij}$ as

$$W'_{ij}|W_{ij}, q_{ij} = \begin{cases} W_{ij}, & q_{ij} \in [\frac{X_{ij}}{10}, 10X_{ij}] \text{ and } W \in [\frac{\nu_i q_{ij}}{10}, 10\nu_i q_{ij}], \\ \nu_{ij}, & \text{otherwise.} \end{cases}$$

Under the setting of Theorem 3, we introduce the following lemmas.

**Lemma 5.** \[\mathbb{E} \log \left( W'_{ij} + \frac{X_{ij} + \lambda_i + 1}{2(1 + \lambda_i)} \right) - \log (\nu_{ij}) \leq 10\frac{\zeta_i}{\nu_{ij}} \text{ holds if } \nu_{ij} \geq C(\delta). \]

**Lemma 6.** \[\mathbb{E} \log^2 \left( W'_{ij} + \frac{X_{ij} + \lambda_i + 1}{2(1 + \lambda_i)} \right) - \log^2 (\nu_{ij}) \leq C \log(\nu_{ij})\frac{\zeta_i}{\nu_{ij}} \text{ holds if } \nu_{ij} \geq C(\delta). \]

**Lemma 7** (Sub-Gaussianity). \[\left\| \sqrt{\frac{\nu_{ij}}{\zeta_{\max}}} \left( \log (W'_{ij} + c_0) - \mathbb{E} \log (W'_{ij} + c_0) \right) \right\|_2 \leq K_0 \text{ for a constant } K_0. \]

**Lemma 8** (Infinity norm bound). Under the setting of Theorem 3 there exists constants $C, C' > 0$, such that

$$\mathbb{P} \left( \| A_W \beta^* - B_W^T y \|_\infty \leq C\sqrt{n \log p \left( \sigma + \left( \frac{p}{b} \zeta_{\max} \right)^{\frac{1}{2}} \|\beta^*\|_1 \right)} \right) \geq 1 - 6p^{-C'}.$$

Applying these lemmas, we can prove Theorem 3 by essentially the same method as the proof of Theorem 1 with $\lambda = C\sqrt{\frac{\log p}{n} \left( \sigma + \left( \frac{p}{b} \zeta_{\max} \right)^{\frac{1}{2}} \|\beta^*\|_1 \right)}$. \[\square\]

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