COMBINING MULTIPLE IMPUTATION WITH RAKING OF WEIGHTS IN THE SETTING OF NEARLY-TRUE MODELS

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ABSTRACT. Raking of weights is one approach to using data from the full cohort in a regression model where some variables of interest are measured only on a subsample. This approach relies on defining an auxiliary variable from the data observed on the whole cohort, which is then used to adjust the weights for the usual Horvitz-Thompson estimator. Computing the optimal raking estimator requires evaluating the expectation of the efficient score given the whole cohort data, which is generally infeasible. We demonstrate the use of multiple imputation as a practical method to compute a raking estimator that will be optimal when the imputation model is correctly specified. We compare this estimator to the common parametric and semi-parametric estimators, including standard multiple imputation. We show that while estimators, such as the semi-parametric maximum likelihood and multiple imputation estimator obtain optimal relative performance under the true model, the raking estimator maintains a better robustness-efficiency trade-off even under mild model misspecification. We demonstrate this property of the proposed raking estimator through several numerical examples and provide a theoretical discussion of conditions for the misspecification that leads to superior asymptotic relative efficiency.

1. Background

Generalized raking is an important technique for using whole population or full cohort information in the analysis of a subsample (Deville and Särndal, 1992, Särndal, 2007, Breslow et al., 2009), closely related to the augmented inverse probability weighted (AIPW) estimators of Robins and co-workers (Robins et al., 1994, Firth and Bennett, 1998, Lumley et al., 2011). The technique is also, and perhaps more commonly, known as “calibration of weights”, but we will avoid that term here because of the potential confusion with other uses of the word “calibration”. An obvious competitor to raking is multiple imputation (Rubin, 1996) of the non-sampled data. While multiple imputation was initially used for relatively small amounts of data missing by happenstance, it has more recently been proposed and used for large amounts of data missing by design, such as when a subsample is taken from a cohort (Marti and Chavance, 2011, Keogh and White, 2013, Jung et al., 2016, Noma et al., 2013).

In this paper we take a different approach, showing how to use multiple imputation to construct new raking estimators that are more efficient than those of Breslow et al. (2009).

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when the imputation model is slightly misspecified, and compare these estimators to direct use of multiple imputation.

Our work has connections to that of Han (2016), who used multiple imputation and empirical likelihood in the missing data paradigm to construct multiply robust estimators that are consistent if any of a set of imputation models or a set of sampling models are correctly specified. We differ in assuming known subsampling probabilities and allowing for a complex sampling design for the full cohort, and in evaluating robustness and efficiency under contiguous (local) misspecification following the “nearly-true models” paradigm of Lumley (2017).

2. Introduction to raking framework

First let us fix notation. We have a full cohort of size $N$ and a probability sample of size $n$ with known sampling probability $\pi_i$ for the $i$-th individual. We observe an outcome variable $Y$, predictors $Z$, and auxiliary variables $A$ on the whole cohort, and observe further predictors $X$ only on the sample. Our goal is to fit a model $P_\theta$ for the distribution of $Y$ given $Z$ and $X$ (but not $A$). The indicator variable for being sampled is $R_i$. We assume an asymptotic setting in which $n \to \infty$ and in which a law of large numbers and central limit theorem exist. In some places we will make the stronger asymptotic assumption that the sequence of cohorts are iid samples from some probability distribution and that the subsamples satisfy $\inf_i \pi_i > \delta > 0$. For comprehensive understanding of the theoretical background, we refer to Breslow et al. (2009), Lumley et al. (2011), Lumley (2017).

With full cohort data with complete observations we would solve an estimating equation

\[ \sum_{i=1}^{N} U(Y_i, X_i, Z_i; \theta) = 0, \]

where $U = U(Y, X, Z; \theta)$ is an estimate of the efficient score or influence function for giving at least locally efficient estimation of $\theta$ with complete data. We write $\hat{\theta}_N$ for the resulting estimator with complete data from the full cohort, and assume it converges in probability to some limit $\theta^*$. If the cohort is truly a realization of the model $P_\theta$, we write $\theta_0$ for the true value of $\theta$. We assume $\theta_N$ would be a locally efficient estimator in the model $P_\theta$ at $\theta_0$, given complete data.

The Horvitz-Thompson-type estimator $\hat{\theta}_{HT}$ of $\theta$ solves

\[ \sum_{i=1}^{N} \frac{R_i}{\pi_i} U(Y_i, X_i, Z_i; \theta) = 0. \]

Under regularity conditions, for example the existence of a central limit theorem and sufficient smoothness for $U$, it is also consistent for $\theta^*$, and thus if $P_\theta$ is correctly specified, for $\theta_0$. 
A generalized raking estimator using an auxiliary variable \( H = H(Y, Z, A; \alpha) \), which may depend on some parameter \( \alpha \), solves a weighted estimating equation

\[
\sum_{i=1}^{N} \frac{g_i R_i}{\pi_i} U(Y_i, X_i, Z_i; \theta) = 0
\]

with adjusted weights \( g_i/\pi_i \). The weight adjustments \( g_i \) are chosen to satisfy the calibration constraints

\[
\sum_{i=1}^{N} \frac{R_i g_i}{\pi_i} H(Y_i, Z_i, A_i; \alpha) = \sum_{i=1}^{N} H(Y_i, Z_i, A_i; \alpha)
\]

while minimizing a distance function \( \sum_{i=1}^{N} d(g_i/\pi_i, 1/\pi_i) \). DeVille and Särndal (1992) uses Lagrange multipliers to construct an iteratively weighted least squares algorithm for computing \( g_i \).

In multiple imputation we use a model for the distribution of \( X \) given \( Z, Y \) and \( A \), but rather than using the expected value of \( X_i \) we take \( M \) samples from the predictive distribution to produce \( M \) imputations \( X_i^{(1)}, \ldots, X_i^{(M)} \), giving rise to \( M \) complete imputed datasets that represent samples from the unknown conditional distribution of the complete data given the observed data. It is now straightforward to solve equation (1) for each of the \( m \)-th imputed dataset, giving \( M \) values \( \hat{\theta}^{(m)} \) with estimated variances \( \sigma^2_{(m)} \), \( 1 \leq m \leq M \). The imputation estimator \( \hat{\theta}_{\text{MI}} \) of \( \theta \) is the average of the \( \hat{\theta}^{(m)} \), and the variance can be estimated from the variance of the \( \hat{\theta}^{(m)} \) and the average of \( \sigma^2_{(m)} \) (Rubin 1996, Eqs 2.1 and 2.2).

### 3. Imputation for Calibration

#### 3.1. Estimation. The optimal function \( H \) is \( E[U|Y, Z, A] \), and using this optimal \( H \) would give the optimal design-consistent estimator of \( \theta \) (Robins et al., 1994), but this \( H \) is typically not available explicitly. Breslow et al. (2009) and Rivera and Lumley (2016) computed a single regression imputation \( \hat{X} \) of \( X \) and solved

\[
\sum_{i=1}^{N} U(Y_i, \hat{X}_i, Z_i; \theta) = 0,
\]

then used the values of \( U_i \) at the solution as the auxiliary variables \( H_i \). We write such a single imputation estimator by \( \hat{\theta}_{\text{cal},1} \).

We propose a raking estimator using multiple imputation. First, solve the sets of equations

\[
\sum_{i=1}^{N} U(Y_i, X_i^{(m)}, Z_i; \theta) = 0,
\]
where $X_1^{(m)}, \ldots, X_N^{(m)}$ are imputed values of $X_i$ for each $m$-th imputation procedure to get multiple estimates $\hat{\theta}_m$, $1 \leq m \leq M$. For each $i$, define $H_i$ as the average of the $M$ resulting $U_i$:

$$
H_i = \frac{1}{M} \sum_{m=1}^{M} U(Y_i, X_i^{(m)}, Z_i; \hat{\theta}_m).
$$

(5)

Finally, we solve (3) with the weight adjustments under the calibration constraint (4), and write the final estimator $\hat{\theta} = \hat{\theta}_{\text{cal},M}$ of $\theta$.

If the regression model $P_\theta$ is correctly specified, and the multiple imputation model is both correctly specified and uses all the available variables, it is clear that the empirical average over imputations in $H_i$ will converge to the optimal value $E[U_i|Y_i, Z_i, A_i]$ as $M$ and $N$ increase, so that $\hat{\theta}$ is the optimal calibration estimator. In the special case where the full cohort is an iid sample and the subsampling is independent (so-called Poisson sampling), Han (2016, Theorem 3) shows $\hat{\theta}$ attains the semiparametric efficiency bound for a model that assumes only $E[U_i] = 0$ and $E[R_i|Z_i, Y_i, A_i] = \pi_i$.

3.2. Efficiency and robustness. When all three of the sampling model, the imputation model, and the regression model are correctly specified, multiple imputation gives a way to compute the efficient design-consistent estimator. However, if we are willing to assume the regression model and imputation model are both correct, there appears to be no motivation for requiring a design-consistent estimator. The multiple imputation estimator $\hat{\theta}_{\text{MI}}$ will also be consistent and will be at least as efficient and typically more efficient. On the other hand, it is unreasonable to assume that the regression and imputation models are exactly correct.

We argue that the interesting questions of robustness and efficiency arise when the imputation model, and potentially also the regression model, are misspecified slightly. More precisely, under what conditions are $\|\hat{\theta}_{\text{cal},M} - \theta^*\|^2$ and $\|\hat{\theta}_{\text{MI}} - \theta^*\|^2$ comparable, and do these correspond to plausible misspecifications of the regression model, the imputation model, or both? These questions were considered in a more abstract context by Lumley (2017), who showed that when the model is only nearly true

$$
\sqrt{n}(\hat{\theta}_{\text{cal},M} - \theta_0) \sim N(0, \sigma^2 + \omega^2)
$$

and

$$
\sqrt{n}(\hat{\theta}_{\text{MI}} - \theta_0) \sim N(\kappa \rho \omega, \sigma^2).
$$

Here, $\kappa$ is the Kullback–Leibler divergence between the true distribution and the closest distribution in the model, with the sequence of misspecified distributions chosen to be contiguous to the model so that $\kappa$ is bounded. $\rho$ is the correlation between the log-likelihood ratio and the difference in the $\hat{\theta}_{\text{cal},M}$ and $\hat{\theta}_{\text{MI}}$ influence functions. The mean-squared error of $\hat{\theta}_{\text{MI}}$ will be larger than that for $\hat{\theta}_{\text{cal},M}$ whenever $|\kappa \rho| > 1$. We study the relative numerical
performance of these two estimators and others under nearly true models in the next section.

4. Simulations

In this section we are interested in three questions; how much precision is gained by multiple versus single imputation in raking, whether imputation models can maintain an efficiency advantage while being more robust, and how these affect the efficiency-robustness trade-off between weighted and imputation estimators. Source code in R for these simulations is available at https://github.com/kyungheehan/calib-mi.

4.1. Case-control study. We first demonstrate numerical performance of multiple imputation for the case-control study where calibration is not available but the maximum likelihood estimator can be easily computed. Let $X$ be a standard normal random variable and $Y$ be a binary response taking values in $\{0, 1\}$ such that for a given $X = x$ the associated logistic model is given by

$$\logit P(Y = 1|X = x) = \alpha_0 + \beta_0 x + \delta(x - \xi)I(x > \xi)$$

for some fixed $\delta$ and $\xi$, and $\logit(p) = \log \left(\frac{p}{1-p}\right)$ for $0 < p < 1$. In accordance with the usual case-control study design, we assume $Y$ is known for everyone, but $X$ is available with sampling probability of 1 when $Y = 1$ and a lower sampling probability when $Y = 0$. To be specific, we first generate a full cohort $X_N = \{(Y_i, X_i) : 1 \leq i \leq N\}$ following the true model (6) and denote the index set of all the $n$-case subjects in $X_N$ by $S_1 \subset \{1, \ldots, N\}$, $n < N$. Thus, $Y_i = 1$ if $i \in S_1$, otherwise $Y_i = 0$. Then a balanced case-control design is employed which consists of observing $(Y_i, X_i)$ for all the subjects in $S_1$ and a randomly chosen $n$-subsample $S_0$ from $\{1, \ldots, N\} \setminus S_1$. For cohort members $\{1, \ldots, N\} \setminus S_0 \cup S_1$, only $Y_i$ is observed. Define $X^*_n = \{(Y_i, X_i) : i \in S_0 \cup S_1\}$.

We examine the sensitivity of the multiple imputation approach in the setting of nearly-true models (Lumley, 2017). For a practical definition of a nearly-true model, we consider a working model that may not be reliably rejected, even when using the oracle test statistic of the likelihood ratio with the true model (6) used to generate the data as the null. In other words, instead of fitting the true model (6), we employ a simpler model

$$\logit P(Y = 1|X = x) = \alpha + \beta x.$$

We note that when $\delta = 0$ the working model (7) is correctly specified, but misspecified when $\delta \neq 0$. It is worthwhile to mention that the single knot linear spline logistic model (6) is the worst case of misspecified model of (7) when $\alpha_0 = -5$, $\beta_0 = 1$ and $\xi \approx 1.8$, which maximizes correlation between the most powerful test to reject the model misspecification and the bias of the misspecified maximum likelihood estimator (Lumley, 2017). In this case, the maximum likelihood estimator of (7) is the unweighted logistic regression (Prentice and Pyke, 1979) for the complete case analysis only with $X^*_n$. 

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Four different methods are compared in our example for estimating the nearly-true slope $\beta$ in (7); (i) the maximum likelihood estimation (MLE), (ii) a design-based inverse probability weighting (IPW) approach, (iii) a multiple imputation with a parametric imputation model (MI-P) and (iv) a multiple imputation with non-parametric imputation based on bootstrap resampling (MI-B). Formally, the parametric MI (MI-P) imputes covariates $X_i, i \notin S_0 \cup S_1$, from a parametric model such that $X|Y = y$ is assumed to be distributed as $N(\mu + \eta y, \sigma^2)$, where $\mu = \mathbb{E}(X|Y = 0), \eta = \mathbb{E}(X|Y = 1) - \mu$, and $\sigma^2 = \text{Var}(X)$. Here, the parameters $\mu, \eta$ and $\sigma^2$ are estimated from $X^n_\ast$. On the other hand, the bootstrap method (MI-B) resamples covariates $X_i, i \notin S_0 \cup S_1$, from the empirical distribution of $X$ given $Y = 0$. We note that MLE only utilizes the sub-cohort information $X^n_\ast$ but the other estimators additionally use response observations $\{Y_i : i \notin S_0 \cup S_1\}$ so that efficiency gains can be expected for estimating the nearly-true slope $\beta$, depending on the level of model misspecification.

Using Monte Carlo iterations, we summarized the empirical performance of the four different estimators based on fitting the nearly-true model (7) with the mean squared error (MSE) of the target parameter $\beta$,

\[ \text{MSE}(\hat{\beta}) = \frac{1}{K} \sum_{k=1}^{K} (\hat{\beta}^{(k)} - \beta)^2, \]

where $\hat{\beta}^{(k)}$ is the estimate of $\beta$ from the $k$-th Monte Carlo replication, $1 \leq k \leq K$. Similarly the empirical bias-variance decomposition,

\[ \text{Bias}(\hat{\beta}) = \mathbb{E}\hat{\beta} - \beta \quad \text{and} \quad \text{Var}(\hat{\beta}) = \frac{1}{K} \sum_{k=1}^{K} (\hat{\beta}^{(k)} - \mathbb{E}\hat{\beta})^2, \]

was also reported to compare precision and efficiency, where $\mathbb{E}\hat{\beta} = K^{-1} \sum_{k=1}^{K} \hat{\beta}^{(b)}$. For all simulations, we fixed $\beta = 1, \alpha_0 = -5, \xi = 1.8, N = 10^4$, and the number of cases was around $n = 110$ in average. We used $M = 100$ multiple imputations and $K = 1000$ Monte Carlo simulations. Results are provided in Table 1.

Table 1 demonstrates two principles. First, the parametric MI (MI-P) estimator closely matches the maximum likelihood estimator, but the resampling (MI-B) estimator closely matches the design-based estimator. Second, more importantly, the design-based estimator is less efficient than the maximum likelihood estimator when the model is correctly specified, but has lower mean squared error when $\delta$ was greater than about 1.6. In this case, even the most powerful one-sided test of the null $\delta = 0$ based on the alternative model (7) would have power less than approximately 0.5, so that any model diagnostic used in a practical setting would have lower power. Figure 1 shows the relative efficiency of the methods as a function of the level of misspecification. In summary, we conclude that the efficiency gain of the model-based analysis is not robust even to mild forms of misspecification that would not be detectable in practical settings.
4.2. **Linear regression with continuous surrogate.** We now evaluate the performance of the multiple imputation raking estimator in a two-phase sampling design. Let $Y$ be a continuous response associated with covariates $X = x$ and $Z = z$ such that

$$\mathbb{E}(Y|X = x, Z = z) = \alpha_0 + \beta_0 x + \delta x \cdot I(|z| > \xi),$$

for some fixed $\delta$ and $\xi = F^{-1}_Z(0.95)$, where $\text{Var}(Y|X, Z) = 1$, $X$ is a standard normal random variable, $Z$ is a continuous surrogate of $X$ and $F^{-1}_Z$ is the inverse cumulative distribution function for $Z$. Similarly to the simulation study in the previous section 4.1, instead of the true model (10) which generally will not be known in a real data setting, we are interested in fitting a typical linear regression model

$$\mathbb{E}(Y|X = x) = \alpha + \beta x.$$

Two different scenarios of the surrogate variable $Z$ are considered such that (a) $Z = X + \varepsilon$ for $\varepsilon \sim N(0, 1)$ and (b) $Z = \eta X$ for $\eta \sim \Gamma(4, 4)$, which represent additive and multiplicative error, respectively. In the first phase of sampling, we assume that outcomes $Y$ and auxiliary variables $Z$ are known for everyone, whereas covariate measurements of $X$ are available only at the second stage. The sampling for the second phase will be stratified on $Z$. Specifically, we will observe $X_i$ for all individuals if $|Z_i| > \xi$, otherwise 5% of subjects in the intermediate stratum $|Z_i| \leq \xi$ are randomly sampled, where $1 \leq i \leq N$. We write $S_2 \subset \{1, \ldots, N\}$ to be the index set of subjects collected in the second phase so that $X_I = \{(Y_i, Z_i) : 1 \leq i \leq N\}$ and $X_{II} = \{(Y_i, X_i, Z_i) : i \in S_2\}$ denote the first and second stage samples, respectively.

We compare five different methods of estimating the nearly-true parameter $\beta$: (i) maximum likelihood estimation (MLE), (ii) a standard generalized raking estimation using the auxiliary variable, (iii) regression calibration (RC), a single imputation method that imputes the missing covariate $X$ with an estimate of $\mathbb{E}[X|Z]$ (Carroll et al., 2006), (iv) multiple imputation without raking (MI), and (v) the proposed approach combining raking and the multiple imputation (MIR). We note that when $Y$ is Gaussian, the semi-parametric efficient maximum likelihood estimator of $\beta$ is available in the missreg3 package in R (Wild and Jiang, 2013), using the stratification information described by Scott and Wild (2006). We employ this for the MLE (i).

For the standard raking method (ii), we construct a design-based efficient estimator (Breslow et al., 2009) as below:

**R1.** Find a single imputation model $X = a + bY + cZ + \epsilon$, where $\epsilon \sim N(0, \tau^2)$ based on the second phase sample $X_{II}$.

**R2.** Fit the nearly-true model (11) using $(Y_i, \hat{X}_i)$ for $1 \leq i \leq N$, where $\hat{X}_i$ are fully imputed from (R1).

**R3.** Calibrate sampling weights for raking using the influence function induced from the nearly-true fits in (R2).
R4. Fit the design-based estimator of the nearly-true model (11) with the second phase sample $X_{II}$ and calibrated sampling weights from (R3).

For the conventional regression calibration approach (iii), we simply fit a linear model regressing $X_i$ on $Z_i$ for $i \in S_i$ and then impute missing observations $\hat{X}_i$ in the first phase so that the nearly-true model (11) is evaluated using $\{(Y_i, \hat{X}_i) : i \not\in S_2\}$ and $\{(Y_i, X_i) : i \in S_2\}$.

We consider two resampling techniques for the multiple imputation method (iv): the wild bootstrap (Cao-Abad, 1991, Mammen, 1993, Hardle and Mammen, 1993) and a Bayesian approach with a non-informative prior. Note, the wild bootstrap gives consistent estimates for settings where the conventional Efron’s bootstrap does not work, such as under heteroscedasticity and high-dimensional settings. We refer to Appendix A.1 for implementation details of multiple imputation with the wild bootstrap and a parametric Bayesian resampling. We now illustrate the proposed method that calibrates sampling weights using multiple imputation.

M1. Resample $\hat{X}_i^*$ independently for all $1 \leq i \leq N$ by using either the wild bootstrap or the parametric Bayesian resampling.

M2. Fit the nearly-true model (11) based on a resample $\{(Y_i, \hat{X}_i^*) : 1 \leq i \leq N\}$.

M3. Repeat (M1) and (M2) in multiple times, and take the average of influence functions, induced by the nearly-true models fitted in (M2).

M4. Calibrate sampling weights using the average influence function as auxiliary information.

M5. Fit the design-based estimator of the nearly-true model (11) with the second phase sample $X_{II}$ and calibrated sampling weights obtained from (M4).

Setting $N = 5000$, we ran $M = 100$ multiple imputations over 1000 Monte Carlo replications. For all simulations, $\beta = 1$, $\alpha_0 = 0$, $\xi \approx 2.3$ when $Z$ is a surrogate of $X$ with an additive measurement error but $\xi \approx 1.8$ with a multiplicative error in our simulation settings, and the phase two sample with $|S_2| = 750$ in average. We considered several values of $\delta$ and the level of misspecification is described by the empirical power to reject the misspecified model for the level 0.05 likelihood ratio test comparing the null (10) and alternative (11).

The numerical results with additive measurement errors are summarized in Table 2 and Figure 2. In this scenario, regression calibration (RC) performed the best for $\delta$ less than approximately 0.15, since RC correctly assumes a linear model for imputing $X$ from $Z$. The two standard multiple imputation had estimation bias due to a misspecified imputation model and had a larger MSE than the RC method. However, we note once again the model diagnostic for linearity, i.e. $\delta = 0$, had at most 20% power for the level of misspecification studied, which means one may not reliably reject the misspecified model even when $\delta = 0.3$ and imputation with the correctly specified model is also unlikely. Indeed the
standard and proposed MIR raking estimators achieved lower MSE when $\delta \geq 0.15$. Thus, raking successfully leveraged the information from the cohort not in the phase two sample while maintaining its robustness, as seen in previous literature (Deville and Särndal, 1992; Särndal, 2007; Breslow et al., 2009). In this simulation we further found that the standard raking estimation efficiency can be improved by using multiple imputation to estimate the optimal raking variable, with efficiency gains of about 10% in this example.

Table 3 and Figure 3 summarize the results for the multiplicative error scenario. In this case, even for $\delta = 0$, the RC and multiple imputations have appreciable bias and worse relative performance compared to the two raking estimators, because of the misspecified imputation model. The two raking estimators outperformed all estimators for all levels of misspecification. In this scenario, the MIR had smaller gains over the standard raking estimator.

5. DATA EXAMPLE: THE NATIONAL WILMS’ TUMOR STUDY

We apply our proposed approach to the data from National Wilms’ Tumor Study (NWTS). In this example, we assume a key covariate of interest is only available in a phase 2 subsample, and compare the proposed MIR method with other standard estimators for this setting. In the data example with NWTS, we are interested in the logistic model for the binary relapse response with predictors histology (UH: unfavorable versus FH: favorable versus), the stage of disease (III/IV versus I/II), age at diagnosis (year) and the diameter of tumor (cm) as

$$\logit P(\text{Relapse} | \text{Histology, Stage, Age, Diameter})$$

$$= \beta_0 + \beta_1(\text{Age}) + \beta_2(\text{Diameter}) + \beta_3(\text{Histology}) + \beta_4(\text{Stage}) + \beta_{3,4}(\text{Histology} \times \text{Stage}),$$

(12)

where $\beta_{3,4}$ indicates an interaction coefficient between histology and stage as in Lumley (2011). We consider (12) is a nearly-true model of the relapse probability associated with covariates, as it is difficult to specify the true model in this real data setting.

Histology was evaluated from both a central laboratory and a local laboratory, where the latter is subject to misclassification due to the difficulty of diagnosing this rare disease. For the first phase data, we suppose that the $N = 3915$ observations of outcomes and covariates are available for the full cohort, except that the histology is obtained only from the local laboratory. Central histology is then obtained on a phase 2 subset. By considering the outcome-dependent sampling strategies as in Breslow and Chatterjee (1999) and Lumley (2011), we sampled individuals for the second phase by stratifying on relapse, local histology and disease stage levels. Specifically, all the subjects who either relapsed or had unfavorable local histology were selected, while only a random subset in the remaining strata (non-relapsed and favorable histology strata for each stage level) were selected so that there was a 1:1 case-control sample for each stage level. We refer to Chapter 8, Lumley (2011) for further details of the two-phase sampling.
Similarly to previous numerical studies, we compared four estimators, where the “true parameters” in (12) are given by estimates from the full cohort analysis: (i) the maximum likelihood estimates (MLE) of the regression coefficients in (12) based on the complete case analysis of the second phase sample; (ii) the standard raking estimator, which calibrates sampling weights by using the local histology information in the first phase sample, where the raking variable was generated by the influence functions. We imputed (unobserved) a central histology path by using a logistic model regressing the second phase histology observations on the age, tumor diameter and three-way interaction among the relapse, stage and local histology together with their nested interaction terms. The reason for introducing interaction in the imputation model is that subjects at advanced disease stage or with unfavorable histology were mostly relapsed in the observed data. It also turned out in our numerical investigation, not reported in this paper, that the proposed imputation model gives superior performance of the raking estimation; (iii & iv) Finally, the conventional bootstrap procedure was employed for multiple imputation (MI) with the second phase sample, and we also combined the raking and multiple imputation (MIR) as proposed in the previous section.

The relative performance of the methods were assessed by obtaining estimates for 1000 two-phase samples. 100 multiple imputations were applied for each two-phase sample. Table 4 summarizes the results. Similarly to the numerical illustration in the previous section, we found that the proposed method (MIR) had the best performance in terms of achieving lowest MSE for the target parameter available only on the subset. While raking does not provide the lowest MSE for all parameters, in this example, MIR had the lowest squared error summed over the model parameters.

6. Discussion

In any practical setting, the chosen statistical model will be at best a close approximation to the targeted true underlying relationship. Freedman (2009) provides a general discussion of the difficulty of testing for model misspecification, demonstrating that the data cannot be used to reliably test even basic model assumptions without good knowledge of the potential structure. Here, we have considered the robustness-efficiency trade of several estimators in the setting of mild model misspecification, where idealized tests with the correct alternative have low power. Lumley (2017) showed when the misspecification is along the least-favorable direction contiguous to the true model, the bias will be in proportion to the efficiency gain from a parametric model. We studied the relative performance of design-based estimators for a nearly-true regression model in two cases, logistic regression in a case-control study and linear regression in a two-phase design, where the misspecification was approximately in the least favorable direction. In both cases, the misspecification took the form of a mild departure from linearity; and in both cases, the raking estimator demonstrated better robustness compared to the parametric MLE and standard multiple imputation models.
Our approach to local robustness is related to that of [Watson and Holmes (2016)], who consider this problem from a Bayesian viewpoint. They argue in favour of estimators that are minimax (under a given loss function) for a Kullback–Leibler neighbourhood of a given model. Our approach is simpler than theirs for two reasons: we consider only asymptotic local minimax behaviour, and we work in a two-phase sampling setting where the sampling probabilities are under the investigator’s control and so can be assumed known. In this setting the optimal raking estimator is consistent and efficient in the sampling model and so is locally asymptotically minimax. In more general settings of non-response and measurement error it is substantially harder to find estimators that are local minimax, even asymptotically, and more theoretical work is needed.

In this work, we also examined the use of multiple imputation to estimate the raking variable that confers the optimal efficiency [Han (2016)]. This proposed raking estimator is easy to calculate and is expected to provided better efficiency than any raking estimator based a single imputation auxiliary variable. In the two cases studied, the improvement in efficiency was evident, though at times small. The degree of improvement of the MI-raking estimator over the standard raking approach is expected to increase with the degree of non-linearity of the score for the target variable. In additional simulations, not shown, we did indeed see larger efficiency gains for MI-raking over single-imputation raking with large measurement error in $Z$.

In many settings, there is a preference to choose simpler models when there is a lack of evidence to support a more complicated approach, because of the clarity of interpretation that the simpler model provides [Box et al. (2005), Stone (1985)]. In such settings, design-based estimators are easy to implement and provide a desired robustness. More theoretical work is also needed to find a more practical representation of the least-favorable contiguous model for the general setting in order to better understand how much of a practical concern this type of misspecification may be. The bias–efficiency tradeoff we describe is also important in the design of two-phase samples. The optimal design for the raking estimator will be different from the optimal design for the efficient estimator, and the optimal design when the outcome model is ‘nearly true’ may be different again.

7. Acknowledgements

This work was supported in part by the Patient Centered Outcomes Research Institute (PCORI) Award R-1609- 36207 and U.S. National Institutes of Health (NIH) grant R01-AI131771. The statements in this manuscript are solely the responsibility of the authors and do not necessarily represent the views of PCORI or NIH.
Table 1. Relative performance of the maximum likelihood (MLE), design-based estimator (IPW), parametric imputation (MI-P) and bootstrap resampling (MI-B) imputation estimators in the case-control design with cohort size \( N = 10^d \), case-control subset with \( n = 110 \) in average, \( M = 100 \) imputations, and 1000 Monte Carlo runs. We report bias, root-mean squared error (\( \sqrt{\text{MSE}} \)), standard error (\( \sqrt{\text{Var}} \)), and the empirical power to reject the nearly-true model through the most powerful (MP) test and the goodness-of-fit test of linear fits (Li and Racine [2007], Hart [2013]).

| \((\beta_0, \delta)\) | Criterion | \(\sqrt{\text{MSE}}\) | \(\text{Bias}\) | \(\sqrt{\text{Var}}\) | Abs Corr† | Empirical power |
|------------------------|-----------|----------------|-------|-------|--------|---------------|
|                        |           | MLE          | IPW   | MI-P  | MI-B   | MP test      | Lin. test     |
| (1, 0)                 | \(\sqrt{\text{MSE}}\) | 0.145        | 0.239 | 0.140 | 0.240  | -            | 0.046         | 0.042         |
|                        | \(\text{Bias}\) | 0.014        | 0.071 | 0.011 | 0.071  | -            | 0.046         | 0.042         |
|                        | \(\sqrt{\text{Var}}\) | 0.144        | 0.229 | 0.140 | 0.229  | -            | 0.046         | 0.042         |
| (0.844, 0.700)         | \(\sqrt{\text{MSE}}\) | 0.148        | 0.229 | 0.147 | 0.229  | 0.427        | 0.202         | 0.042         |
|                        | \(\text{Bias}\) | -0.067       | 0.064 | -0.077| 0.064  | 0.427        | 0.202         | 0.042         |
|                        | \(\sqrt{\text{Var}}\) | 0.132        | 0.219 | 0.125 | 0.219  | 0.427        | 0.202         | 0.042         |
| (0.692, 1.400)         | \(\sqrt{\text{MSE}}\) | 0.199        | 0.217 | 0.204 | 0.217  | 0.431        | 0.410         | 0.061         |
|                        | \(\text{Bias}\) | -0.156       | 0.054 | -0.168| 0.054  | 0.431        | 0.410         | 0.061         |
|                        | \(\sqrt{\text{Var}}\) | 0.124        | 0.211 | 0.116 | 0.211  | 0.431        | 0.410         | 0.061         |
| (0.541, 2.100)         | \(\sqrt{\text{MSE}}\) | 0.257        | 0.201 | 0.262 | 0.201  | 0.342        | 0.683         | 0.156         |
|                        | \(\text{Bias}\) | -0.233       | 0.047 | -0.242| 0.047  | 0.342        | 0.683         | 0.156         |
|                        | \(\sqrt{\text{Var}}\) | 0.109        | 0.196 | 0.102 | 0.195  | 0.342        | 0.683         | 0.156         |
| (0.381, 2.800)         | \(\sqrt{\text{MSE}}\) | 0.317        | 0.206 | 0.320 | 0.206  | 0.268        | 0.905         | 0.382         |
|                        | \(\text{Bias}\) | -0.301       | 0.056 | -0.306| 0.056  | 0.268        | 0.905         | 0.382         |
|                        | \(\sqrt{\text{Var}}\) | 0.098        | 0.199 | 0.093 | 0.199  | 0.268        | 0.905         | 0.382         |
| (0.241, 3.5)           | \(\sqrt{\text{MSE}}\) | 0.368        | 0.192 | 0.368 | 0.192  | 0.297        | 0.978         | 0.645         |
|                        | \(\text{Bias}\) | -0.358       | 0.049 | -0.359| 0.049  | 0.297        | 0.978         | 0.645         |
|                        | \(\sqrt{\text{Var}}\) | 0.083        | 0.185 | 0.080 | 0.185  | 0.297        | 0.978         | 0.645         |

†The absolute value of the correlation between \( \hat{\beta}_{\text{MLE}} - \hat{\beta}_{\text{IPW}} \) and \( \Delta = \sqrt{\text{log} P_n - \text{log} Q_n} \), where \( P_n \) and \( Q_n \) are likelihood functions at \( \theta^P = (\alpha_0, \beta_0, \delta) \) and \( \theta^Q = (\alpha, \beta) \), respectively.
Table 2. Multiple imputation in two-stage analysis with continuous surrogates when $Z = X + \varepsilon$ for independent $\varepsilon \sim N(0, 1)$. We compare relative performance of the maximum likelihood (MLE), standard raking, regression calibration (RC), multiple imputations (MI) using either the wild bootstrap or Bayesian approach, and the proposed multiple imputation with raking (MIR) estimators for a two-phase design with cohort size $N = 5000$, phase 2 subset $|S_2| = 750$ in average, $M = 100$ imputations, and 1000 Monte Carlo runs. We report bias, root-mean squared error ($\sqrt{\text{MSE}}$), standard error ($\sqrt{\text{Var}}$), and the empirical power to reject the nearly-true model through the most powerful (MP) test and the goodness-of-fit test of linear fits (Hart [2013], Li and Racine [2007]). See the Appendix for implementation details of the goodness-of-fit test.

| $(\beta_0, \delta)$ | Criterion | MLE | Raking | RC | MI | MI | MIR | Abs Corr† | Empirical power |
|---------------------|-----------|-----|--------|----|----|----|-----|---------|-----------------|
|                     |           |     |        |    |    |    |     |         | MP test | Lin. test     |
| (1, 0)              | $\sqrt{\text{MSE}}$ | 0.019 | 0.038  | 0.017 | 0.019 | 0.019 | 0.034 | 0.034   | -     | 0.052   | 0.065 |
|                     | Bias      | 0.004 | 0.000  | 0.000 | 0.002 | -0.003 | 0.001 | 0.001   | -     | -       | -     |
|                     | $\sqrt{\text{Var}}$ | 0.019 | 0.038  | 0.017 | 0.018 | 0.018 | 0.034 | 0.034   | -     | -       | -     |
| (0.951, 0.068)      | $\sqrt{\text{MSE}}$ | 0.033 | 0.037  | 0.022 | 0.023 | 0.026 | 0.033 | 0.033   | -     | -       | -     |
|                     | Bias      | -0.027 | 0.000  | -0.014 | -0.014 | -0.019 | 0.001 | 0.001   | 0.480  | 0.140   | 0.078 |
|                     | $\sqrt{\text{Var}}$ | 0.018 | 0.037  | 0.017 | 0.018 | 0.018 | 0.033 | 0.033   | -     | -       | -     |
| (0.904, 0.131)      | $\sqrt{\text{MSE}}$ | 0.058 | 0.036  | 0.032 | 0.034 | 0.039 | 0.033 | 0.033   | -     | -       | -     |
|                     | Bias      | -0.056 | 0.000  | -0.027 | -0.029 | -0.034 | 0.001 | 0.001   | 0.496  | 0.407   | 0.089 |
|                     | $\sqrt{\text{Var}}$ | 0.018 | 0.036  | 0.017 | 0.018 | 0.018 | 0.033 | 0.033   | -     | -       | -     |
| (0.861, 0.191)      | $\sqrt{\text{MSE}}$ | 0.084 | 0.036  | 0.042 | 0.047 | 0.052 | 0.032 | 0.032   | -     | -       | -     |
|                     | Bias      | -0.082 | -0.001 | -0.038 | -0.043 | -0.048 | 0.001 | 0.001   | 0.497  | 0.698   | 0.108 |
|                     | $\sqrt{\text{Var}}$ | 0.018 | 0.036  | 0.017 | 0.018 | 0.018 | 0.032 | 0.032   | -     | -       | -     |
| (0.820, 0.247)      | $\sqrt{\text{MSE}}$ | 0.108 | 0.035  | 0.052 | 0.059 | 0.064 | 0.032 | 0.032   | -     | -       | -     |
|                     | Bias      | -0.107 | 0.000  | -0.049 | -0.057 | -0.062 | 0.001 | 0.001   | 0.496  | 0.893   | 0.142 |
|                     | $\sqrt{\text{Var}}$ | 0.017 | 0.035  | 0.017 | 0.018 | 0.018 | 0.032 | 0.032   | -     | -       | -     |
| (0.781, 0.3)        | $\sqrt{\text{MSE}}$ | 0.132 | 0.035  | 0.062 | 0.072 | 0.077 | 0.032 | 0.032   | -     | -       | -     |
|                     | Bias      | -0.131 | -0.001 | -0.060 | -0.069 | -0.074 | 0.001 | 0.001   | 0.495  | 0.978   | 0.189 |
|                     | $\sqrt{\text{Var}}$ | 0.017 | 0.035  | 0.017 | 0.018 | 0.018 | 0.032 | 0.032   | -     | -       | -     |

†The absolute value of the correlation between $\hat{\beta}_{\text{MLE}} - \hat{\beta}_{\text{Raking}}$ and $\log Q_n - \log P_n$, where $P_n$ and $Q_n$ are likelihood functions at $\theta^P = (\alpha_0, \beta_0, \delta)$ and $\theta^Q = (\alpha, \beta)$, respectively.
Table 3. Multiple imputation in two-stage analysis with continuous surrogates when $Z = \eta X$ for independent $\eta \sim \Gamma(4, 4)$. We compare relative performance of the maximum likelihood (MLE), standard raking, regression calibration (RC), multiple imputations using (MI) either the wild bootstrap or Bayesian approach, and the proposed multiple imputation with raking (MIR) estimators for a two-phase design with cohort size $N = 5000$, phase 2 subset $|S_2| = 750$ in average, $M = 100$ imputations, and 1000 Monte Carlo runs. We report bias, root-mean squared error ($\sqrt{\text{MSE}}$), standard error ($\sqrt{\text{Var}}$), and the empirical power to reject the nearly-true model through the most powerful (MP) test and the goodness-of-fit test of linear fits [Hart, 2013; Li and Racine, 2007]. See the Appendix for implementation details of the goodness-of-fit test.

| $(\beta_0, \delta)$ | Criterion | Abs Corr† | Empirical power |
|---------------------|-----------|-----------|-----------------|
|                     |           | MLE Raking RC MI Boot Bayes MIR Boot Bayes MP test Lin. test |
| $(1, 0)$            | $\sqrt{\text{MSE}}$ | 0.018 0.030 0.216 0.099 0.094 | 0.029 0.029 | - 0.048 0.056 |
|                     | Bias      | 0.006 0.001 0.215 0.097 0.092 | 0.002 0.002 | - 0.048 0.056 |
|                     | $\sqrt{\text{Var}}$ | 0.017 0.030 0.013 0.018 0.018 | 0.029 0.029 | - 0.048 0.056 |
| $(1.045, -0.068)$   | $\sqrt{\text{MSE}}$ | 0.040 0.030 0.227 0.111 0.106 | 0.029 0.029 | - 0.048 0.056 |
|                     | Bias      | 0.036 0.001 0.227 0.109 0.104 | 0.002 0.002 | 0.565 0.149 0.062 |
|                     | $\sqrt{\text{Var}}$ | 0.018 0.030 0.013 0.018 0.018 | 0.029 0.029 | - 0.048 0.056 |
| $(1.087, -0.131)$   | $\sqrt{\text{MSE}}$ | 0.068 0.031 0.239 0.123 0.117 | 0.030 0.030 | - 0.048 0.056 |
|                     | Bias      | 0.065 0.001 0.238 0.121 0.116 | 0.002 0.002 | 0.584 0.427 0.075 |
|                     | $\sqrt{\text{Var}}$ | 0.018 0.031 0.013 0.018 0.018 | 0.030 0.030 | - 0.048 0.056 |
| $(1.127, -0.191)$   | $\sqrt{\text{MSE}}$ | 0.095 0.032 0.249 0.134 0.128 | 0.031 0.031 | - 0.048 0.056 |
|                     | Bias      | 0.093 0.001 0.249 0.133 0.127 | 0.002 0.002 | 0.585 0.697 0.099 |
|                     | $\sqrt{\text{Var}}$ | 0.018 0.032 0.014 0.018 0.018 | 0.030 0.031 | - 0.048 0.056 |
| $(1.165, -0.247)$   | $\sqrt{\text{MSE}}$ | 0.121 0.032 0.259 0.144 0.139 | 0.031 0.031 | - 0.048 0.056 |
|                     | Bias      | 0.119 0.001 0.259 0.143 0.138 | 0.002 0.002 | 0.583 0.890 0.136 |
|                     | $\sqrt{\text{Var}}$ | 0.019 0.032 0.014 0.019 0.019 | 0.031 0.031 | - 0.048 0.056 |
| $(1.200, -0.3)$     | $\sqrt{\text{MSE}}$ | 0.146 0.033 0.269 0.155 0.149 | 0.032 0.032 | - 0.048 0.056 |
|                     | Bias      | 0.145 0.001 0.268 0.154 0.148 | 0.003 0.002 | 0.580 0.967 0.179 |
|                     | $\sqrt{\text{Var}}$ | 0.019 0.033 0.014 0.019 0.019 | 0.032 0.032 | - 0.048 0.056 |

†The absolute value of the correlation between $\hat{\beta}_{\text{MLE}} - \hat{\beta}_{\text{Raking}}$ and $\log Q_n - \log P_n$, where $P_n$ and $Q_n$ are likelihood functions at $\theta^P = (\alpha_0, \beta_0, \delta)$ and $\theta^Q = (\alpha, \beta)$, respectively.
Table 4. The National Wilms Tumor Study data example. We compare relative performance of the maximum likelihood (MLE), standard raking, multiple imputation (MI) using the wild bootstrap (MI), and the proposed multiple imputation with raking (MIR) estimators for a two-phase design with cohort size $N = 3915$, phase 2 subset $|S_2| = 1338$, $M = 100$ imputations, and 1000 Monte Carlo runs. We report bias, root-mean squared error ($\sqrt{\text{MSE}}$), standard error ($\sqrt{\text{Var}}$), where bias is calculated relative to the full cohort parameter estimates in the nearly-true model (12).

| Method | Criterion | $\sqrt{\text{MSE}}$ | Bias | $\sqrt{\text{Var}}$ | $\text{Var}$ | $\text{Bias}$ | $\sqrt{\text{Var}}$ | $\text{Var}$ | $\text{Bias}$ | $\sqrt{\text{Var}}$ | $\text{Var}$ | $\text{Bias}$ | $\sqrt{\text{Var}}$ |
|---------|-----------|---------------------|------|---------------------|-------------|-------------|---------------------|-------------|-------------|---------------------|-------------|-------------|---------------------|
| MLE     | $\sqrt{\text{MSE}}$ | 1.768               | 0.777 | 0.014               | 0.014       | 0.605       | 4.096               | 0.031       | 0.023       | 0.013               | 0.008       | 0.051       | 0.005               |
|         | Bias      | -1.768              | -0.777 | -0.007              | -0.012      | 0.603       | 4.091               | 0.129       | 0.022       | 0.006               | 0.003       | 0.203       | 0.059               |
|         | $\sqrt{\text{Var}}$ | 0.031               | 0.023 | 0.013               | 0.008       | 0.051       | 0.005               | 0.127       | 0.022       | 0.006               | 0.003       | 0.197       | 0.056               |
| Raking  | $\sqrt{\text{MSE}}$ | 0.146               | 0.015 | 0.003               | 0.002       | 0.175       | 0.052               | 0.135       | 0.015       | 0.002               | 0.001       | 0.170       | 0.047               |
|         | Bias      | 0.055               | -0.004 | 0.003               | 0.002       | -0.042      | 0.005               | 0.124       | 0.022       | 0.006               | 0.003       | 0.189       | 0.051               |
|         | $\sqrt{\text{Var}}$ | 0.031               | 0.023 | 0.013               | 0.008       | 0.051       | 0.005               | 0.127       | 0.022       | 0.006               | 0.003       | 0.197       | 0.056               |
| MI      | $\sqrt{\text{MSE}}$ | 0.146               | 0.015 | 0.003               | 0.002       | 0.175       | 0.052               | 0.135       | 0.015       | 0.002               | 0.001       | 0.170       | 0.047               |
|         | Bias      | 0.055               | -0.004 | 0.003               | 0.002       | -0.042      | 0.005               | 0.124       | 0.022       | 0.006               | 0.003       | 0.189       | 0.051               |
|         | $\sqrt{\text{Var}}$ | 0.031               | 0.023 | 0.013               | 0.008       | 0.051       | 0.005               | 0.127       | 0.022       | 0.006               | 0.003       | 0.197       | 0.056               |
| MIR     | $\sqrt{\text{MSE}}$ | 0.124               | 0.022 | 0.006               | 0.003       | 0.189       | 0.051               | 0.122       | 0.021       | 0.006               | 0.003       | 0.185       | 0.049               |
|         | Bias      | 0.018               | 0.006 | 0.001               | 0.001       | -0.038      | 0.002               | 0.012       | 0.022       | 0.006               | 0.003       | -0.038      | 0.002               |
|         | $\sqrt{\text{Var}}$ | 0.031               | 0.023 | 0.013               | 0.008       | 0.051       | 0.005               | 0.127       | 0.022       | 0.006               | 0.003       | 0.197       | 0.056               |
| Full cohort | Estimate  | 1.193               | 0.285 | 0.089               | 0.028       | 0.816       | -                   | 0.156       | 0.105       | 0.017               | 0.012       | 0.227       | -                   |
|         | Std. Error | 0.156               | 0.105 | 0.017               | 0.012       | 0.227       | -                   | 0.156       | 0.105       | 0.017               | 0.012       | 0.227       | -                   |

1 Unfavorable histology versus favorable; 2 disease stage III/IV versus I/II; 3 year at diagnosis; 4 tumor diameter(cm); 5 Histology*Stage.
Figure 1. Illustration of Table I. Relative performance of the maximum likelihood (MLE), design-based estimator (IPW), parametric imputation (MI-P) and bootstrap resampling (MI-B) imputation estimators in the case-control design.
Figure 2. Illustration of Table 2. Relative performance of the maximum likelihood (MLE), standard raking, regression calibration (RC), multiple imputations (MI) using either the wild bootstrap or Bayesian approach, and the proposed multiple imputation with raking (MIR) estimators in two-stage analysis with continuous surrogates when \( Z = X + \varepsilon \) for independent \( \varepsilon \sim N(0,1) \).
Figure 3. Illustration of Table 3. Relative performance of the maximum likelihood (MLE), standard raking, regression calibration (RC), multiple imputations (MI) using either the wild bootstrap or Bayesian approach, and the proposed multiple imputation with raking (MIR) estimators in two-stage analysis with continuous surrogates when $Z = \eta X$ for independent $\eta \sim \Gamma(4, 4)$. 

\[
\begin{array}{cccccc}
\text{MSE} & 0.00 & 0.10 & 0.20 & 0.30 \\
0.000 & -0.068 & -0.131 & -0.247 & \delta \\
0.048 & 0.149 & 0.427 & 0.697 & 0.89 & 0.967 \\
\text{Power (MP)} & 0.056 & 0.062 & 0.075 & 0.099 & 0.136 & 0.179 (linearity test) \\
\end{array}
\]
A.1. **Imputation.** The wild bootstrap multiple imputation estimator is computed as follows:

W1. Generate $X^*_i = \hat{X}_i + V_i \hat{e}_i$ for $i \in S_2$, where $\hat{e}_i$ are residuals from (R2) and $V_i$ is an independent dichotomous random variable that takes on the value $(\sqrt{5} - 1)/(2\sqrt{5})$ otherwise $(1 - \sqrt{5})/2$, so that $\mathbb{E} V = 0$ and $\text{Var}(V) = 1$.

W2. Find an imputation model regressing $X^*_i$ on $Y_i$ and $Z_i$ for $i \in S_2$.

W3. Resample $\hat{X}_i^* \sim N(\nu(Y_i, Z_i), \tau^2(Y_i, Z_i))$ independently for $i \in S_1$, where the mean and variance functions $\nu(Y_i, Z_i) = \mathbb{E}(X|Y = y, Z = z)$ and $\tau^2(Y_i, Z_i) = \text{Var}(X|Y = y, Z = z)$ are estimated from the model in (W2).

W4. Fit the nearly-true model (11) using $\{(Y_i, \hat{X}_i^*) : 1 \leq i \leq N\}$, where $\hat{X}_i^* = X_i$ for $i \in S_2$.

W5. Repeat (W1)–(W4) and take the average of multiple estimates of parameters.

We employ a parametric Bayesian resampling technique as follows:

B1. Find a posterior distribution of parameters $(a, b, c, \tau^2)$ for the imputation model used in (R1) given the second phase sample $X_{II}$.

B2. Generate $(a^*, b^*, c^*, \tau^2_*)$ from the posterior distribution in (B1).

B3. Resample $X_i^* \sim N(a^* + b^*Y_i + c^*Z_i, \tau^2_*)$ independently for $i \in S_1$.

B4. Fit the nearly-true model (11) using $\{(Y_i, \hat{X}_i^*) : 1 \leq i \leq N\}$, where $\hat{X}_i^* = X_i$ for $i \in S_2$.

B5. Repeat (B1)–(B4) and take the average of multiple estimates of parameters.

For the prior distribution of $(a, b, c, \tau^2)$, we adopt a non-informative prior $p(a, b, c, \tau^2) \propto 1/\tau^2$. In (B2), we first generate $\tau^2_2|X_{II} \sim \Gamma^{-1}(a_n/2, b_n/2)$, where $a_n = |S_2| - 3$ and $b_n$ is the residual sum of squares from the linear regression model. Then, we generate $(a^*, b^*, c^*)^\top \tau^2_2, X_{II} \sim N_{d}(\hat{a}, \hat{b}, \hat{c})^\top, \tau^2_2(\Xi^\top \Xi)^{-1})$, where $\Xi$ is the design matrix of the linear regression model in (R1) and $(\hat{a}, \hat{b}, \hat{c})$ is the corresponding estimate of the regression coefficient.

A.2. **The goodness-of-fit test.** We use the wild bootstrap [Cao-Abad, 1991, Mammen, 1993, Hardle and Mammen, 1993] together with kernel smoothing techniques in testing model specification of the parametric model. Suppose the true model is given by

\[ Y = m(X; \theta) + \varepsilon, \]

where $m$ is a known function depending of the parameter $\theta$ and $\varepsilon$ is a noise uncorrelated to $X$, that is $\mathbb{E}(\varepsilon|X) = 0$. In our study, we are mainly interested in testing the null
hypothesis such that

\[ H_0 : m(X; \theta) = \alpha + \beta X \ (a.e.) \]

for some \( \theta = (\alpha, \beta)^\top \in \mathbb{R}^2 \). We note that under the null hypothesis \( H_0 \), estimation of \( E(Y|X = \cdot) \) in a fully nonparametric way regressing i.i.d. observations \( Y_i \) on \( X_i \), \( 1 \leq i \leq n \), is less efficient than we directly fit the parametric model (13) based on the same sample. However, fitting the parametric model may suffers from inevitable bias when the model is misspecified as the sample size is increasing. We refer to [Hart (2013)] and [Li and Racine (2007)] for more comprehensive ideas on statistical hypothesis tests with nonparametric approach.

From the above observation, we may test if the mean squared error quantifying the goodness-of-fit of the specified model (13) is small compared to the nonparametric fits. Specifically, we measure

\[ \ell_n = \text{MSE}(\hat{\theta}) - \text{MSE}(\hat{m}) \]

and examine if the observed quantity \( \ell_n \) is significantly small, where \( \hat{m}(\cdot) \) is a univariate kernel regression estimator of \( E(Y|X = \cdot) \).

Here, we choose the bandwidth for kernel smoothing based on leave-one-out cross validation criterion which empirically optimizes prediction performance of the kernel smoothed estimates and it can be easily implemented by using the npregbw function of the np package in R (Racine and Hayfield, 2018). Similarly to the previous ideas of the bootstrap resampling, the p-value of testing the null hypothesis \( H_0 \) is computed as below:

1. Generate \( Y^*_i = \hat{\alpha} + \hat{\beta} X_i + V_i \hat{\epsilon}_i \), \( 1 \leq i \leq n \), where \( \hat{\epsilon}_i = Y_i - \hat{\alpha} + \hat{\beta} X_i \) and \( V_i \) are random copies of an independent random variable \( V \) which takes binary values by \((1 + \sqrt{5})/2 \) with probability \((\sqrt{5} - 1)/(2\sqrt{5})\), otherwise \((1 - \sqrt{5})/2 \) so that \( E V = 0 \) and \( \text{Var}(V) = 1 \).

2. Fit the parametric model with \((Y^*_1, X_1), \ldots, (Y^*_n, X_n)\) and let \( \hat{\theta}^* = (\hat{\alpha}^*, \hat{\beta}^*)^\top \) be the resulting estimate of the parameter \( \theta \). Compute the mean squared error \( \text{MSE}(\hat{\theta}^*) = n^{-1} \sum_{i=1}^n(Y^*_i - \hat{\alpha}^* - \hat{\beta}^* X_i)^2 \).

3. Find kernel smoothed fits \( \hat{Y}^* = \hat{m}^*(X_i) \), \( 1 \leq i \leq n \), and compute the mean squared error \( \text{MSE}(\hat{m}^*) = n^{-1} \sum_{i=1}^n(Y^*_i - \hat{m}^*(X_i))^2 \).

4. Repeat (L1)–(L3) independently to obtain \( \ell^*_n = \text{MSE}(\hat{\theta}^*) - \text{MSE}(\hat{m}^*) \) in multiple times to get an empirical distribution of \( \ell_n \).

5. Compute the empirical p-value as the fraction of events \( \ell^*_n > \ell_n \) occurred among repeated runs in (L4).

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