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Robust likelihood-based analysis of multivariate data with missing values

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Abstract

The model-based approach to inference from multivariate data with missing values is reviewed. Regression prediction is most useful when the covariates are predictive of the missing values and the probability of being missing, and in these circumstances predictions are particularly sensitive to model misspecification. The use of penalized splines of the propensity score is proposed to yield robust model-based inference under the missing at random (MAR) assumption, assuming monotone missing data. Simulation comparisons with other methods suggest that the method works well in a wide range of populations, with little loss of efficiency relative to parametric models when the latter are correct. Extensions to more general patterns are outlined.
KEYWORDS: double robustness, incomplete data, penalized splines, regression imputation, weighting

1. Introduction

Missing values arise in empirical studies for many reasons. For example, in longitudinal studies, data are missing because of *attrition*, when subjects drop out prior to the end of the study. In most surveys, some individuals provide no information because of non-contact or refusal to respond (*unit* nonresponse). Other individuals are contacted and provide some information, but fail to answer some of the questions (*item* nonresponse). Often indices are constructed by summing values of particular items. For example, in economic studies, total net worth is a combination of values of individual assets or liabilities, some of which may be missing. If any of the items that form the index are missing, some procedure is needed to deal with the missing data.

The missing data *pattern* simply indicates which values in the data set are observed and which are missing. Specifically, let $Y = (y_{ij})$ denote an $(n \times p)$ rectangular dataset without missing values, with ith row $y_i = (y_{i1}, \ldots, y_{ip})$ where y_{ij} is the value of variable Y_j for subject *i*. With missing values, the pattern of missing data is defined by the *missing-data indicator matrix* $M = (m_{ij})$ with ith row $m_i = (m_{i1}, \ldots, m_{ip})$, such that $m_{ij} = 1$ if y_{ij} is missing and $m_{ij} = 0$ if y_{ij} is present. We assume throughout that (y_i, m_i) are independent over *i*.

Some methods for handling missing data apply to any pattern of missing data, whereas other methods assume a special pattern. For simplicity we consider methods for the simple pattern of *univariate* nonresponse, where missingness is confined to a single variable, say Y_p, and $Y_1, \ldots, Y_{p-1}$ are fully observed. In Section 7 we discuss extensions of our methods to more general patterns, such as *monotone* missing data, where the variables can be arranged so that $Y_{j+1}, \ldots, Y_p$ is missing for all cases where Y_j is missing, for all j = 1, ..., p-1. This pattern arises commonly in longitudinal data subject to attrition.

The performance of alternative missing-data methods depends strongly on the missing-data mechanism, which concerns the reasons why values are missing, and in particular whether missingness depends on the values of variables in the data set. For example, subjects in a longitudinal intervention may more likely to drop out of a study because they feel the treatment was ineffective, which might be related to a poor value of an outcome measure. Rubin (1976) treated M as a random matrix, and characterized the missing-data mechanism by the conditional distribution of M given Y, say $f(M|Y, f)$, where f denotes unknown parameters. When missingness does not depend on the values of the data Y, missing or observed, that is:

$$f(M|Y, f) = f(M|f) \text{ for all } Y, f,$$

the data are called missing completely at random (MCAR). With the exception of planned missing-data designs, MCAR is a strong assumption, and missingness often does depend on recorded variables. Let Y_{obs} denote the observed values of Y and Y_{mis} the missing values. A less restrictive assumption is that missingness depends only on values Y_{obs} that are observed, and not on values Y_{mis} that are missing. That is:

$$f(M \mid Y, f) = f(M \mid Y_{obs}, f) \text{ for all } Y_{mis}, f .$$

The missing data mechanism is then called missing at random (MAR). Many methods for handling missing data assume the mechanism is MCAR or MAR, and yield biased estimates when the data are not MAR (NMAR).

The main ideas of this article can be summarized in the following propositions:

(a) When the missing data mechanism is unknown and NMAR, methodological options are limited and not very appealing to the practitioner. Thus, in studies where missing data are likely to arise, efforts should be made to render the MAR assumption plausible, by measuring covariates that characterize nonrespondents (Little and Rubin, 1999).

(b) The most useful covariates for nonresponse adjustment are (i) predictive of the missing values Y_{mis} and (ii) predictive of the missing data indicator *M*. Of the two, criterion (i) is the most important, since conditioning on a covariate that is predictive of *M* but not of Y_{mis} can lead to a loss of efficiency. Section 3 presents an analysis in support of these statements.

(c) All missing-data adjustments require modeling assumptions relating the missing data to observed covariates. Sensitivity to assumptions is a particularly serious issue for analysis involving covariates that are useful for missing-data adjustments, as described in (b).

(d) Given (a) - (c), missing-data methods based on MAR and models that make relatively weak assumptions relating the covariates to the missing data are useful. Methods of this kind based on propensity splines are proposed in Sections 4 and 5 below, for the special case of univariate

nonresponse. These methods are assessed by simulation in Section 6. Some extensions of these methods to more general missing data problems are outlined in Section 7, and Section 8 presents concluding remarks.

2. Limitations of NMAR analyses when the missing data mechanism is unknown.

An extensive literature of methods for NMAR missing-data mechanisms has been developed; early examples include Heckman's (1976) proposals for handling selectivity bias, and Rubin's (1977) Bayesian analysis. See also Little and Rubin (2002, chapter 15). The difficulty of the problem can be seen by considering the simplest situation of a single variable Y_1 (that is, $p = 1$), observed for r cases and missing for $n - r$ cases, with no covariate information. Suppose the respondent values of Y_1 are independently distributed with mean μ_{1R} and variance σ_{11}, and the nonrespondent values are independently distributed with mean μ_{1NR} and variance σ_{11}. If the observations are independent, then MCAR=MAR, and $\mu_{1R} = \mu_{1NR}$. In that case, the sample mean $\bar{y}_1$ based on the r complete cases is unbiased, and in many cases optimal for the mean. If, on the other hand, the data are NMAR, the bias of $\bar{y}_1$ for inference about the overall mean is easily seen to be $f\,l\,\sigma_{11}^{1/2}$, where $f = (n-r)/n$ is the fraction of missing values and $l = (\mu_{1R} - \mu_{1NR})/\sigma_{11}^{1/2}$ is the standardized difference in respondent and nonrespondent means. Assuming asymptotic normality and ignoring t corrections, the noncoverage rate of the usual 95% confidence interval $\bar{y}_1 \pm 1.96\sqrt{s_{11}/r}$ based on the complete cases is

$$\Phi(-1.96 + \sqrt{r}\,f\,l) + \Phi(-1.96 - \sqrt{r}\,f\,l),$$

Table 1. Coverage of 95% confidence interval for population mean when the respondent mean has a bias $f l = 0.1$.

Respondent sample size	20	50	100	200
Coverage rate (%)	7.4	10.9	18.0	29.2

where Φ denotes the normal cumulative density function. Table 1 tabulates this noncoverage rate as a function of the respondent sample size *r*, for a fixed bias of $f l = 0.1$. Clearly bias has an increasing distorting effect on the noncoverage as the sample size increases.

Analysis options are clearly limited in the absence of information about the nonrespondents. Other than assuming the bias away, the only other option is to widen the interval to allow for potential bias. Three approaches to this are

(a) To develop bounds for the quantity of interest that include all possible values of the missing data. For example, for a binary outcome, one might calculate the sample proportion with all missing values imputed as one, and all missing values imputed as zero (Horowitz and Manski, 2000). This approach tends to be very conservative, and is limited to variables that have finite support.

(b) Conduct a sensitivity analysis for alternative models for nonignorable nonresponse (Rubin, 1977; Little and Wang, 1996; Scharfstein, Rotnitsky and Robins, 1999).

(c) Add a prior distribution for the nonrespondent values and apply the Bayesian paradigm. For example, Rubin (1977) considers the model:

$$m_{1R} \sim \text{const.};\ m_{1NR} \mid m_{1R} \sim N(m_{1R}, l s_{11})$$

An alternative approach is to attempt to measure covariates that capture differences between respondents and nonrespondents, so that the missing-data mechanism can be considered MAR. For the remainder of this paper we consider models under the assumption that the missing

data are MAR, while recognizing that residual dependence of the missing data indicators on missing values of the data may require one of the approaches (a) - (c) delineated above.

3. Covariates to the rescue?

Suppose now that fully observed covariates are available, and let $Y_1,...Y_{p-1}$ denote the variables observed for all *n* cases, and Y_p the variable with missing values, observed for the first *r* cases. The mean of Y_p can be written as

$$m_p = E[(1-M)Y_p] + E[ME(Y_p \mid X)],$$

and $E[(1-M)Y_p]$ can be estimated from the complete cases. To estimate the second term $E[ME(Y_p \mid X)]$, note that under MAR, $E(Y_p \mid X) = E(Y_p \mid X, M = 0) = E(Y_p \mid X, M = 1)$. Hence for incomplete cases ($M = 1$) one can estimate $E(Y_p \mid X)$ from the complete cases and predict the *Y* for each incomplete case by substituting the *X* for that case into the regression formula. If the regression is linear, this leads to the regression estimate:

$$\hat{m}_p = n^{-1}\left(\sum_{i=1}^{r} y_{ip} + \sum_{i=r+1}^{n} \hat{y}_{ip} \right) \qquad (1)$$

where $\{y_{ip}, i = 1,...,r\}$ are the observed values of Y_p, and $\hat{y}_{ip} = \hat{b}_0 + \sum_{j=1}^{p-1} \hat{b}_j y_{ij}$ is the prediction from the regression of Y_p on $(Y_1,...,Y_{p-1})$, computed on the *r* complete cases. Eq. (1) is the maximum likelihood (ML) estimate of m_p for a variety of models, including multivariate normality for $(Y_1,...,Y_p)$ (e.g., see Little and Rubin, 2002).

The impact of regressing on covariates for inference about m_p can be assessed by comparing the mean squared error of $\hat{m}_p$ relative to the estimate based on the complete cases,

$\bar{y}_p = \sum_{i=1}^{r} y_{ip} / r$. Consider this comparison for a single covariate (p = 2), where Y_1 and Y_2 are bivariate normal, and the missing data are MAR. The regression estimate (1) is then unbiased for m_2 with mean squared error (e.g. Little and Rubin, 2002)

$$mse(\hat{m}_2) = (s_{22} / r)\left((1 - r^2) + (r/n)\, r^2 + (1 - r^2)(1 - r/n)^2 \Delta^2\right),$$

ignoring $O(1/r^2)$ terms, where r is the correlation between respondent values of Y_1 and Y_2, and Δ is the difference in the nonrespondent and respondent mean of Y_1, divided by the respondent variance of Y_1. Note the r^2 measures the association between Y_1 and Y_2 and Δ^2 measures the association between Y_1 and M. The mean squared error of $\bar{y}_2$ is

$$mse(\bar{y}_2) = (s_{22} / r) + (1 - r/n)^2 \Delta^2 r^2 s_{22},$$

where the first term on the right side is the variance and the second term is the bias. Subtracting and simplifying yields

$$mse(\bar{y}_2) - mse(\hat{m}_2) = (1 - r/n) s_{22}\left[(1 - r/n) r^2 \Delta^2 + r^2/r - (1 - r/n)(1 - r^2)\Delta^2 / r\right]. \qquad (2)$$

The first term in the square parenthesis in Eq. (2) is $O(1)$ and the bias that has been eliminated by the regression of Y_2 on Y_1 (more generally under NMAR one expects the regression to reduce bias, although it could increase). Both r^2 and Δ^2 must be large for this term to be substantial. The second and third terms in the square parenthesis represent variance reduction from the regression on Y_1. This variance reduction is substantial when r^2 is large. In fact, if r^2 is small and Δ^2 is large, as when Y_1 is predictive of M but not predictive of Y_2, the net value of these terms may be negative, reflecting an increase in variance from the regression on Y_1. These results are summarized in Table 2. Eq. (2) generalizes to a multivariate set of predictors, with the

Table 2. Effect on bias and variance of the estimated mean of Y_2 of regression on a fully-observed covariate Y_1, for combinations of the association between Y_1 and Y_2 (r^2) and the association between Y_1 and M (Δ^2).

	r^2 Low	r^2 High
Δ^2 Low	bias change: ≈ 0 variance change: ≈ 0	bias change : ≈ 0 variance change: $\downarrow$
Δ^2 High	bias change: ≈ 0 variance change: $\uparrow$	bias change : $\downarrow$ variance change: $\downarrow$

obvious generalizations of r^2 and Δ^2. Clearly, the key for both bias and variance reduction is that Y_1 is a good predictor of Y_2.

4. Robust MAR inference with a single covariate

4.1. Robust Prediction

In the previous section we noted that the key to reduce mean squared error for inference about the mean of Y_p is to find predictors that are predictive of Y_p and the missing data indicator *M*. These are the circumstances under which inference are most sensitive to misspecification of the regression of Y_p on $Y_1,...,Y_{p-1}$, since the bias reduction is dependent on an appropriate specification of the model relating Y_p to $Y_1,...,Y_{p-1}$. Thus we now consider robust alternatives to the linear additive model (1). We first consider the case of a single covariate, $p = 2$. Extensions to more than one covariate are discussed in Sections 5 and 7.

Standard regression modeling methods, such as adding polynomial terms and interactions to the regression in (1), are useful strategies. Perhaps the simplest way to weaken assumptions

about the relationship between Y_2 and a continuous covariate Y_1 is to group the covariate into categories and regress on dummy variables for the categories. The resulting regression estimate,

$$\hat{m}_2 = \sum_{c=1}^{C} p_c \bar{y}_{c2} , \tag{3}$$

is the average of the respondent mean $\bar{y}_{c2}$ in each category weighted by the sample proportion $p_c = n_c / n$ in that category.

An attractive alternative to categorization of continuous covariates is to fit a smooth but relatively nonparametric relationship between Y_2 and the covariate (Cheng, 1994). For example, one might model the regression of Y_2 on Y_1 via a penalized spline (Eilers and Marx, 1996, Ruppert and Carroll, 2000) with a power-truncated spline basis:

$$y_{i2} = spline\left(y_{i1}\right) + e_i = b_0 + \sum_{j=1}^{q} b_j y_{i1}^j + \sum_{k=1}^{K} b_{q+k} \left(y_{i1} - t_k\right)_+^q + e_i, \quad e_i \sim N\left(0, s^2\right), \tag{4}$$

where q is the degree of polynomial, $\left(x\right)_+^q = x^q I\left(x \geq 0\right)$, $t_1 < \cdots < t_K$ are selected fixed knots, and K is the total number of knots. Then, the penalized least-squares estimator $\hat{b} = \left(\hat{b}_0, \ldots, \hat{b}_{q+K}\right)^{\mathrm{T}}$ can be obtained by minimizing the penalized sum of squared errors

$$\sum_{i=1}^{n} \left\{ y_{i2} - b_0 - \sum_{j=1}^{q} b_j y_{i1}^j - \sum_{k=1}^{K} b_{q+k} \left(y_{i1} - t_k\right)_+^q \right\}^2 + l \sum_{k=1}^{K} b_{q+k}^2 ,$$

where l is the smoothing parameter. The smoothing parameter can be estimated by generalized cross validation or by ML for a linear mixed model, treating $\left(b_0, \ldots, b_q\right)^{\mathrm{T}}$ as a fixed parameter vector and $\left(b_{q+1}, \ldots, b_{q+K}\right)^{\mathrm{T}}$ as a random vector. Cheng (1994) achieves nonparametric smoothing by another method, kernel regression; an attractive feature of the ML version of penalized splines is that they are easily implemented with widely available software such as PROC MIXED in SAS (SAS, 1992) and lme( ) in S-plus (Pinheiro and Bates, 2000).

4.2. Weighting the complete cases.

An alternative to prediction, commonly used for unit nonresponse adjustments in sample surveys, is to weight the complete cases by the inverse of an estimate of the probability of response (e.g. Little and Rubin, 2003, Section 3.3). The mean of Y_2 can be written as:

$$m_2 = E\left[\frac{(1-M)Y_2}{w(Y_1)}\right] / E\left[\frac{1-M}{w(Y_1)}\right],$$

where $w(Y_1) = \Pr(M = 0 \mid Y_1)$ is the probability that Y_2 is observed given Y_1. The denominator in this equation can be ignored since it equals one under correct specification of the $w(Y_1)$. Replacing population quantities by sample estimates yields the weighted complete-case estimate:

$$\hat{m}_2 \equiv \bar{y}_{2w} = \left(\sum_{i=1}^{r} w_i y_{i2}\right) / \left(\sum_{i=1}^{r} w_i\right), \tag{5}$$

or

$$\hat{m}_2 \equiv \bar{y}_{2w} = \left(\sum_{i=1}^{r} w_i y_{i2}\right) / n, \tag{5A}$$

where the weight w_i for respondents is an estimate of $w(y_{i1})$. If Y_1 is grouped into categories, and respondents in category c are weighted by the inverse of the estimated response rate r_c / n_c in category c, then the resulting estimator (5) or (5A) is identical to the regression estimate (3). Note that if the true response rate is the same for all the categories c, as when the data are MCAR, then weighting by the true response rate yields the unweighted sample mean $\bar{y}_2$ based on the complete cases, which is less efficient if the categorized covariate is predictive of response. This is a simple and instructive illustration of increased efficiency when weights are estimated from the sample rather than from population parameters (e.g. Robins, Rotnitsky and Zhao, 1994).

In section 4.1 we used splines to smooth the predictions from a regression model. A different use of smoothing is to smooth the weights in the weighted estimator (5). That is, the

weights are replaced by the inverse of the estimated propensity to respond, computed by fitting a spline to the logistic regression of the missing-data indicator M on Y_1.

$$\begin{aligned} w_i &= 1/\hat{p}_i, \hat{p}_i = \hat{\Pr}(M_i = 1 \mid y_{i1}), \\ \text{logit}\left(\hat{p}_i\right) &= spline(y_{i1}), \end{aligned} \tag{6}$$

where a spline for the binary outcome analogous to (5) can be fitted using a generalized linear mixed model (Breslow and Clayton, 1993). These two approaches to smoothing for prediction and weighting are compared in the simulations in Section 6.

4.3. Calibration estimators

The mean of Y_2 can be written in a way that combines the features of prediction and weighting:

$$m_2 = E\left[\frac{(1-M)}{w(Y_1)}(Y_2 - E(Y_2 \mid Y_1)\right] + E[E(Y_2 \mid Y_1)].$$

Estimating quantities in this expression leads to a "calibration" estimator of the form

$$\hat{m}_2 = n^{-1}\left(\sum_{i=1}^{r} w_i (y_{i2} - \hat{y}_{i2})\right) + n^{-1}\left(\sum_{i=1}^{n} \hat{y}_{i2}\right). \tag{7}$$

where the predictions $\hat{y}_{i2}$ from the model are calibrated by adding a term consisting of weighted residuals from the model. Variants of this estimator replace the predictions for the respondents by observed values, and the denominator n of the sum of weighted residuals by the sum of the weights. The estimator with both these features is

$$\hat{m}_2 = \left(\sum_{i=1}^{r} w_i (y_{i2} - \hat{y}_{i2})\right) / \left(\sum_{i=1}^{r} w_i\right) + n^{-1}\left(\sum_{i=1}^{r} y_{i2} + \sum_{i=r+1}^{n} \hat{y}_{i2}\right). \tag{7A}$$

The estimator (7) has properties of semi-parametric efficiency and "double-robustness" (Robins, Rotnitsky and Zhao, 1994; Robins and Rotnitsky, 2001), in the sense that the estimate is consistent if just one of the models for prediction or weighting are correctly specified. We conjecture but do not prove similar properties for (7A). However, since the calibration of the

predictions is to correct effects of model misspecification, we believe that the calibration of the predictions in Eq. (7) or (7A) is unnecessary if the prediction model does not make strong parametric assumptions, as in (4). This conjecture is supported by the simulation studies in Section 6.

5. Robust MAR Inferences with More than One Covariate

With sufficient sample size, a penalized spline provides a useful model for predictions based on a single covariate. With several covariates an additive model might be fitted with splines on the continuous covariates. In particular, Scharfstein and Izzary (2003) consider the estimator (7) where the propensity score model and mean model follow generalized additive regressions. However, this approach requires larger samples and is subject to misspecification error if interactions are present. We propose here a prediction model that addresses the "curse of dimensionality" by focusing the spline on a particular function of the covariates most sensitive to model misspecification, namely the propensity score. Suppose that Y_p is subject to missing values and $Y_1,...,Y_{p-1}$ are fully observed covariates, and $p \geq 3$ so that there are at least 2 covariates. We first define the logit of the propensity score for Y_p to be observed, given the covariates $Y_1,...,Y_{p-1}$:

$$Y_p^* = \text{logit}\left(\Pr(M = 0 \mid Y_1,...,Y_{p-1})\right). \quad (8)$$

The key property of the propensity score is that conditional on the propensity score and assuming MAR, missingness of Y_p does not depend on $Y_1,...,Y_{p-1}$ (Rosenbaum and Rubin, 1983). Thus the mean of Y_p can be written as:

$$m_p = E[(1-M)Y_p] + E[M \times E(Y_p \mid Y_p^*)] .$$

This motivates (a) estimating Y_p^* by a logistic regression of M on $(Y_1,...,Y_{p-1})$, yielding estimated propensity $\hat{Y}_p^*$, and then (b) predicting the missing values of Y_p by a spline of $\hat{Y}_p^*$. Since variables other than $\hat{Y}_p^*$ may be good predictors of Y_p, the other covariates are entered in the regression parametrically, for example as linear additive terms. That is, the prediction model for missing values of Y_p has mean function

$$E(Y_p \mid Y_p^*, Y_2,...,Y_{p-1}) = spline(\hat{Y}_p^*) + \sum_{j=2}^{p-1} b_j Y_j . \quad (9)$$

We call Eq. (9) a propensity spline prediction model. It differs from the simple additive linear model of Y_p on $Y_1,...,Y_{p-1}$ in Eq. (1) in that one of the covariates (say Y_1) has been replaced by the estimated propensity $\hat{Y}_p^*$ and modeled using a spline. The remaining covariates do not include Y_1 to avoid multicollinearity. Of course nonlinear terms in $Y_2,...Y_{p-1}$ and interactions involving $Y_2,...Y_{p-1}$ and $\hat{Y}_p^*$ could be added to (9), but these are excluded for reasons of parsimony. The main idea is to focus on specifying the relationship with the propensity score correctly, since misspecification of that relationship leads to bias.

The idea of explicitly including the propensity score as a covariate in the prediction model was previously proposed by David et al. (1983) and in a more general context in Robins (1999). The use of a spline on the propensity is an application of Yu and Ruppert's (2002) partially linear single-index model in the missing-data setting. The prediction estimator based on (9) is robust in the sense that if either (a) the prediction model (9) is correctly specified, or (b) the propensity $\hat{Y}_p^*$ is correctly specified and the mean of Y_p given $\hat{Y}_p^*$ is correctly modeled by the

spline in (9), then the prediction estimator is consistent for m_p. Specifically for (b), consider the prediction of missing values via an estimator of the form:

$$\hat{Y}_p(g) = spline(Y_p^*) + \sum_{j=1}^{k} b_j \left[g_j(Y_2,...,Y_{p-1}) - E\left(g_j(Y_2,...,Y_{p-1}) \right) \right], \quad (10)$$

where $g_j(Y_1,...,Y_{p-1})$ are arbitrary functions of covariates $Y_2,...,Y_{p-1}$ that have been transformed to be independent of Y_p^*. These functions are centered by their means in (10). Then taking the expectation of (10) over the distribution of $Y_2,...Y_{p-1}$ given Y_p^*,

$$E(\hat{Y}_p(g) \mid Y_p^*) = spline(Y_p^*), \quad (11)$$

since $Y_2,...,Y_{p-1}$ are independent of Y_p^*. If the regression of Y_p on Y_p^* is correctly specified by the spline function, then

$$spline(Y_p^*) = E(Y_p \mid Y_p^*), \quad (12)$$

and assuming MAR,

$$E(Y_p \mid Y_p^*) = E(Y_p \mid Y_p^*, M = 1), \quad (13)$$

by the property of propensity scores mentioned above. Hence (11)-(13) imply that

$$E(\hat{Y}_p(g) \mid Y_p^*) = E(Y_p \mid Y_p^*, M = 1),$$

which means that the prediction estimator based on (10) is consistent; consistency is maintained when Y_p^* is replaced by a consistent estimate $\hat{Y}_p^*$. This robustness property is consistent with the results of the simulation study in the next section, which compares the properties of this approach with alternatives.

6. Simulations

We conducted two simulation studies to examine the performance of the estimators of the mean of Y with missing data under MAR. In the first simulation study, we consider only one fully observed covariate Y_1 and one variable Y_2 with missing values. We generated Y_1 from a uniform distribution between –1 and 1, and Y_2 from a normal distribution with one of four mean structures:

(I) constant : $N\left(6, 2^2\right)$,

(II) linear : $N\left(6+10Y_1, 2^2\right)$,

(III) cubic: $N\left(-4+5\left(1+Y_1\right)^3, 2^2\right)$, and

(IV) sine : $N\left(6+15\sin\left(p\,Y_1\right), 2^2\right)$.

The expected value of Y_2 is 6 for four mean structures, and (II) – (IV) model a strong predictive relationship between Y_1 and Y_2. We also consider four different response structures for the propensity to respond:

(I) constant (MCAR) : $\text{logit}\left(pr\left(M=0\,|\,Y_1\right)\right)=0.5$,

(II) linear : $\text{logit}\left(pr\left(M=0\,|\,Y_1\right)\right)=3Y_1$,

(III) cubic : $\text{logit}\left(pr\left(M=0\,|\,Y_1\right)\right)=3Y_1^3$, and

(IV) sine: $\text{logit}\left(pr\left(M=0\,|\,Y_1\right)\right)=1.5\sin\left(p\,Y_1\right)$ where $\text{logit}\left(x\right)=\log\left(x/\left(1-x\right)\right)$.

The response rate for all these propensity structures is 0.5, and (II) – (IV) model a strong predictive relationship between Y_1 and M. The simulation is thus focused on the fourth cell of Table 2, when a well-specified regression adjustment has strong gains. For each combination of mean and propensity structure, 500 simulated data sets with sample size n=100 were generated.

Then, six different estimators of mean of Y_2 are compared with the mean of Y_2 before deletion (BD), namely:

(CC) The complete-case estimate, deleting the incomplete cases;

(LP) The prediction estimator (1) based on linear regression;

(SP) The prediction estimator (1) based on a penalized spline regression model (4);

(LW) The weighted estimator (5) with weights computed as the inverse of the response propensity estimated by linear logistic regression of the missing-data indicator on Y_1;

(SW) The weighted estimator (5) with weights computed as the inverse of the response propensity estimated by spline logistic regression of the missing-data indicator on Y_1, as in (6);

(SPW) The calibration estimator (7) with predictions computed as for SP and weights computed as for SW. The estimator (7A) was also computed but yielded very similar results, and hence is omitted to save space.

For the penalized splines methods, we chose 20 equally spaced fixed knots over Y_1 and a truncated linear basis.

The results from this simulation study are summarized in Table 3. For each combination of mean structure and response propensity structure and each estimator, the standardized bias

STDBIAS = 100×(bias/empirical standard error),

is tabulated, where bias is the deviation of the average estimate over the 500 simulated data sets from the true parameter value, and the empirical standard error is standard deviation of the estimates over the 500 simulated data sets. Also the relative root mean squared error compared with the BD estimator

RRMSE = 100×(RMSE(estimator) – RMSE(BD))/RMSE(BD)

is tabulated, where RMSE is the square root of the average squared deviation of the estimate from the true value over the 500 simulated data sets. We conclude the following from Table 3:

(1) A crude summary of the overall performance of the methods is obtained by averaging the RRMSE over all 16 problems. These average values (ordered from best to worst) are:

SP: 23, SPW: 25, SW: 35, LW: 42, LP: 47, CC: 207.

Hence on the average, CC is much worse than the other methods, SP and SPW are the best methods, and SW, LW and LP are intermediate.

(2) Bias calibration does not appear to have much payoff for SP, since the bias of that method is relatively minor. In fact SPW has similar or slightly higher RRMSE than SP for all problems considered.

(3) When Y_1 and Y_2 are independent none of the methods display bias, as theory would predict. When the mechanism is MCAR, the RRMSE's of all the methods are very similar; when the mechanism is MAR, CC analysis is best, followed by LP and SP, which are in turn more efficient than the weighting approaches LW, SW and SPW. For all the other mean models CC analysis has a large bias when the data are not MCAR, and is not competitive with other methods.

(4) When Y_1 and Y_2 are linearly related, LP is the best method, as predicted by theory, but SP is nearly as good, showing little loss in efficiency. LW and SW are noticeably inferior in this case.

(5) When Y_1 and Y_2 are not linearly related and data are not MCAR, LP predictably suffers from bias from model misspecification; SP does much better in these cases since it is not based on a linearity assumption.

(6) When the model for the propensity is not linear, there is some evidence that SW is better than LW, consistent with the fact that SW does not make a linearity assumption for the logit of the propensity. However gains are less dramatic than for SP over LP.

In summary, the spline prediction approach appears to be the best method overall, emerging as best or close to best in all the situations simulated.

In the second simulation study, we have two fully observed covariates Y_1 and Y_2, and one variable Y_3 with missing values. We generated Y_1 and Y_2 as independent uniform deviates between –1 and 1, and Y_3 from a normal distribution with one of four mean structures:

(I) constant: $N(10, 2^2)$,

(II) linear : $N(10(1+Y_1+3Y_2), 2^2)$,

(III) additive : $N(118+(3Y_1-3)^3+(3Y_2-3)^3, 2^2)$,

(IV) non-additive : $N(10(1+Y_1+Y_2+4Y_1Y_2), 2^2)$.

The expected value of Y_3 for all these mean structures is 10. We simulated four response propensity structures, all of which yield an expected response rate of 0.5:

(I) constant : $\text{logit}(pr(M=0|Y_1,Y_2))=0.5$,

(II) linear : $\text{logit}(pr(M=0|Y_1,Y_2))=Y_1+Y_2$,

(III) additive : $\text{logit}(pr(M=0|Y_1,Y_2))=Y_1^3+Y_2^3$,

(IV) non-additive : $\text{logit}(pr(M=0|Y_1,Y_2))=Y_1+Y_2+3Y_1Y_2$.

For each combination of these mean and propensity structures, 500 simulated data sets with sample size *n*=100 are generated. Then, we compared the mean before deletion (BD) with the following eight estimators of the mean of Y_3 from the incomplete data:

(CC) The complete-case mean;

(LP) Regression prediction from a linear regression of Y_3 on Y_1 and Y_2;

(ASP) The prediction estimator (1) based on an additive regression model of Y_3 on penalized splines for Y_1 and Y_2;

(LW) The weighted estimator (5) with weights computed as the inverse of the response propensity estimated by linear logistic regression of the missing-data indicator on Y_1 and Y_2;

(ASW) The weighted estimator (5) with weights computed as the inverse of the response propensity estimated by an additive spline logistic regression of the missing-data indicator on Y_1 and Y_2;

(ASPW) The calibration estimator (7) with predictions computed as for ASP and weights computed as for ASW. Results for the estimator (7A) were very similar and are omitted to save space.

(SPP) Penalized spline propensity prediction based on a regression of Y_3 on the spline of Y_3^*, the linear predictor of the estimated propensity to respond from a linear logistic regression of M on Y_1, Y_2; that is, Eq. (9) without linear parametric terms;

(SPPL) Penalized spline propensity prediction based on Eq. (9) with a linear parametric term for Y_2.

We choose 15 equally spaced knots over Y_1 and Y_2 respectively and a truncated linear basis for the ASW and ASPW. We also choose 20 equally spaced knots over the estimated response propensity and a linear truncated basis for the SPP and SPPL.

Results in Table 4 can be summarized as follows:

(1) Again as a rough indication, the RRMSE's of each method averaged over problems are:

SPP: 28; SPPL: 30; LP: 43; ASP: 44; ASPW: 45; LW: 54; ASW: 57; CC: 133

Thus the propensity spline methods do best overall; the other prediction methods, LP, ASP and ASPW, are similar and not quite as good; the weighting methods, LW and ASW, have somewhat higher RRMSE than LP and ASP; CC is much worse than the other methods.

(2) The superior overall performance of SPP and SPPL is mainly attributable to better bias and RMSE when both the mean model and the propensity model are non-additive. In that case the additive models are misspecified, and the calibration estimator is also biased because of lack of additivity in the response propensity model. In fact all the methods appear to be biased for this rather demanding problem, but the propensity spline methods have less bias than the others.
(3) Little gain was seen from adding Y_2 to the propensity spline, since SPP and SPPL performed very similarly. Greater gains might be expected in problems with more useful covariates.
(4) The ASP method works very well when the mean model is linear or additive, so the additivity assumption holds. Calibration of this method has little effect, since the results for ASPW are very similar to those of ASP. These results are consistent with those of the first simulation; however this method becomes more demanding with more than two covariates, and as noted above does rely on additivity assumptions.
(5) As in the first simulation, the weighting methods LW and ASW are less efficient than the prediction methods, and smoothing the weight by a spline does not appear to help much.

The results of any simulation study are limited by the choice of populations simulated, but our conclusion from these two simulations is that the propensity spline methods are an attractive way of conditioning on observed covariates without making strong assumptions about the mean structure.

7. Extensions to Monotone and General Patterns

The propensity spline model of the previous section extends in an obvious way to a monotone pattern of missing data, where the variables can be arranged such that Y_j is more observed than Y_{j+1}, for $j = 1,..., p-1$. Missing values are filled in as conditional means from the following sequence of regressions:

Y_2 on $spline\left(\hat{w}_2(Y_1)\right)$

Y_3 on $spline\left(\hat{w}_3(Y_1, Y_2)\right), Y_2$

…

Y_p on $spline\left(\hat{w}_p(Y_1,..., Y_{p-1})\right), Y_2,..., Y_{p-1}$,

where $\hat{w}_j(Y_1,..., Y_{j-1})$ is the estimated propensity that Y_j is observed given $Y_1,..., Y_{j-1}$, estimated by a logistic regression of the missing-data indicator for Y_j on $Y_1,..., Y_{j-1}$. Missing values of covariates are replaced by their predictions in this sequence of regressions. Multiple imputation versions of this approach, where draws from the predictive distribution are imputed rather than means, and extensions to general patterns of missing data based on the sequential imputation methods of Raghunathan et al. (2001), will be examined in future research.

8. Conclusions

Despite the large literature devoted to nonignorable missing data adjustments, we believe that the key to successful treatment of missing data is to measure covariates that are predictive of the missing values, and careful modeling of the relationships between the missing variables and these covariates. Likelihood-based methods based on multivariate models for the data are useful

tools for making efficient use of the available data, but standard models such as the multivariate normal imply linear additive relationships between the variables that may be too simplistic in certain settings. Easily-fitted spline models are proposed here to yield regression predictions that are more robust to nonlinearity in the relationship between the missing variables and the covariates, under the MAR assumption. A key idea is to single out the propensity score for this robust form of modeling.

A limitation of the work on propensity spline methods described here is that it is focuses on point estimation. Inferences for the propensity spline prediction model require valid estimates of standard errors, and ideally Student t corrections for small samples. Possible approaches to computing standard errors include:

(a) computing the estimate on a set of bootstrap samples, and calculating a bootstrap standard error from the sample variance over the bootstrap samples, or from percentiles of the bootstrap distribution;

(b) ignoring sampling error in estimating the propensity $\hat{w}(Y_1,...,Y_{p-1})$, and using asymptotic standard errors for the model (9) based on standard linear mixed model formulae.

(c) using the propensity spline prediction model to multiply-impute draws from the predictive distribution of the missing values, and then using multiple imputation methods for estimating the variance (e.g. Rubin, 1987; Little and Rubin, 2002, chapter 10).

Simulations comparing these approaches are currently under investigation. Future work will also consider extensions to general patterns of missing data, based on extensions of the sequential imputation method of Raghunathan et al. (2001).

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Table 3. Simulation Study Comparing Estimators with a Single Covariate.

Propensity Model→		Constant (MCAR)(I)		Linear (II)		Cubic (III)		SINE (IV)	
↓ Mean Model		STDBIAS	RRMSE	STDBIAS	RRMSE	STDBIAS	RRMSE	STDBIAS	RRMSE
Constant (I)	BD	-3	0	0	0	1	0	-4	0
	CC	-3	25	-5	40	1	39	-4	35
	LP	-3	25	-8	85	1	53	-6	45
	SP	-3	25	-9	94	0	55	-6	48
	LW	-3	25	-6	115	0	52	-6	52
	SW	-3	25	-5	107	0	54	-6	54
	SPW	-3	25	-8	116	-1	58	-5	55
Linear (II)	BD	6	0	1	0	4	0	2	0
	CC	8	36	504	493	286	293	269	295
	LP	5	5	3	15	3	9	3	10
	SP	5	5	3	18	2	10	3	10
	LW	6	5	11	92	23	19	-26	43
	SW	6	5	22	79	32	27	9	22
	SPW	5	5	3	23	2	11	3	11
Cubic (III)	BD	-4	0	6	0	6	0	2	0
	CC	-1	28	383	466	247	333	228	239
	LP	-6	6	-149	147	-68	53	-38	13
	SP	-4	2	0	11	-1	3	0	3
	LW	-3	6	17	42	16	5	-13	5
	SW	-4	3	25	42	27	12	12	11
	SPW	-4	2	2	11	0	3	1	3
SINE (IV)	BD	6	0	-2	0	-1	0	-5	0
	CC	5	24	430	421	168	160	408	395
	LP	6	12	50	75	-79	61	182	144
	SP	6	1	-43	65	-20	10	-1	3
	LW	6	12	-2	33	-87	52	156	114
	SW	6	11	5	31	-51	32	72	39
	SPW	6	1	-42	65	-19	10	-2	3

Table 4. Simulation Study Comparing propensity spline prediction other methods.

Propensity Model →		Constant (MCAR) (I)		Linear (II)		Additive (III)		Non-Additive (IV)	
↓ Mean Model		STDBIAS	RRMSE	STDBIAS	RRMSE	STDBIAS	RRMSE	STDBIAS	RRMSE
Constant (I)	BD	5	0	-4	0	-4	0	1	0
	CC	7	35	-3	42	-6	48	0	52
	LP	7	36	-5	57	-6	57	-5	56
	ASP	7	36	-3	60	-6	58	-5	58
	LW	7	36	-4	61	-6	56	-6	66
	ASW	7	36	-4	62	-5	57	-7	71
	SPP	7	36	-4	59	-5	57	-5	59
	SPPL	7	36	-3	59	-5	57	-5	59
	ASPW	7	37	-3	64	-4	59	-5	66
Linear (II)	BD	1	0	5	0	3	0	-8	0
	CC	-1	25	232	240	147	137	168	188
	LP	1	1	5	1	3	1	-8	1
	ASP	1	1	5	1	3	1	-8	1
	LW	2	1	6	25	3	5	-113	82
	ASW	2	1	11	25	9	6	-111	90
	SPP	1	1	4	4	1	2	-22	5
	SPPL	1	1	5	1	3	1	-8	1
	ASPW	1	1	5	1	3	1	-8	1
Additive (III)	BD	-5	0	2	0	8	0	-3	0
	CC	-2	25	272	264	180	166	191	233
	LP	-3	5	38	21	36	16	24	25
	ASP	-5	0	3	0	9	0	-2	1
	LW	-6	5	7	48	19	30	-91	134
	ASW	-5	3	15	40	25	26	-103	141
	SPP	-5	4	10	11	24	9	51	40
	SPPL	-5	3	10	11	22	7	70	40
	ASPW	-5	0	3	0	9	0	-2	1
Non-Additive (IV)	BD	2	0	-2	0	-7	0	7	0
	CC	6	35	116	154	71	90	303	393
	LP	5	28	-82	113	-35	55	221	215
	ASP	5	30	-80	131	-34	67	222	243
	LW	5	27	-6	33	-5	30	250	218
	ASW	5	28	-2	33	-4	34	253	224
	SPP	5	18	-11	22	-6	19	154	106
	SPPL	5	19	-10	29	-5	24	151	125
	ASPW	6	29	-18	90	-13	59	236	308