ORIGINAL ARTICLE

Using the Prognostic Score to Reduce Heterogeneity in Observational Studies

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Summary

In large sample observational studies, the control population often greatly outnumbers the treatment population. Typical practice is to match several control observations to a single treated observation, with the goal of reducing variability of the resulting treatment effect estimate. However, increasing the control to treated ratio yields diminishing returns in terms of variance reduction and in practice leads to poorer quality matches. In line with Rosenbaum’s argument on the importance of reducing heterogeneity to strengthen causal inference against unobserved bias, we suggest first expending some of the controls to fit a prognostic model, then matching with the resulting prognostic score to produce matched sets with lower heterogeneity. We propose methodological alternatives for fitting the prognostic model that help avoid concerns of overfitting and extrapolation, then we demonstrate in a simulation setting how this alternative use of the control observations can lead to gains in terms of both treatment effect estimation and design sensitivity.

KEYWORDS: causal inference, observational studies, matching, propensity score, prognostic score, Fisher-Mill plots

1 INTRODUCTION

Unlike in a randomized experiment, any claim of a causal effect based on observational data must address the possibility of bias stemming from non-random treatment assignment. Matching methods attempt to adjust for this bias by recreating a randomized experiment, grouping treatment and control subjects in a way that balances the observed covariates’ distributions. However, matching does not guarantee balance in the unobserved covariates; practitioners typically carry out their analyses making the unverifiable assumption that all the relevant covariates have been observed. Performing a sensitivity analysis provides a way to quantify how robust the results, derived under assumptions of conditional ignorability, are to the presence of unobserved bias.

Propensity score matching and Mahalanobis distance matching, the two most popular matching metrics for causal inference, can be seen as recreating two different kinds of experimental designs: the completely randomized experiment and the fully blocked randomized experiment, respectively. A completely randomized experiment will still lead to an unbiased estimate of the treatment effect; However a fully blocked randomized experiment, which attempts to control for sources of nuisance variation by assigning subjects to homogeneous blocks, will tend to be more statistically efficient. In the context of randomized experiments, increasing the sample size and reducing the within-block heterogeneity play interchangeable roles, since both reduce the sampling variability of the treatment effect estimate. Surprisingly, this experimental intuition does not carry over to

Abbreviations: ATE, average treatment effect; ATT, average treatment effect among the treated; MSE, mean squared error.
observational studies. In fact, in the observational setting, reducing within-matched set heterogeneity has the added benefit of reducing sensitivity to unobserved bias, which cannot be achieved through increasing the sample size alone.[5]

In light of this result, it would seem that Mahalanobis distance matching, which attempts to match on all the observed covariates at once, should result in matches that are less sensitive to unobserved bias than propensity score matching, which only attempts to match on a score involving covariates that are predictive of receiving the treatment. However, Mahalanobis distance matching is known to suffer from the curse of dimensionality. Since in large dimensions all observations are in some sense “far away” from each other, this method is forced to compromise on poorer quality matches.[5]

The less commonly used prognostic score, formalized by Hansen,[7] models the subject’s expected response had they not received treatment, based on the observed covariates. Matching on this quantity reflects the experimental ideal of controlling for systematic variation in the response under control settings, which should reduce within-matched set heterogeneity compared to propensity score matching. Analogous to the propensity score, the prognostic score can reduce the covariates to a scalar quantity and – under suitable assumptions – results in a form of covariate balance which leads to valid inference. The primary difference is that the prognostic score emphasizes covariates based on how predictive they are of the response, while the propensity score emphasizes covariates based on how predictive they are of the treatment assignment.

Unfortunately, matching on the prognostic score poses several challenges not encountered when matching on the propensity score. First, when using the propensity score, we can directly assess whether covariate balance holds for the observed data. In contrast, when using the prognostic score, we cannot assess whether prognostic balance holds for the treatment group, since we do not observe the counterfactual responses of the treatment group had they not received the treatment. Another challenge is that same-sample estimation of the prognostic score tends to cause overfitting to the control group, biasing estimation of treatment effects.[8,9] Furthermore, if the set of controls used to fit the prognostic model are far from the treatment group in terms of their covariates, estimating the prognostic score for the treated observations requires extrapolation.

To help mitigate these issues with the prognostic score, Hansen recommends matching jointly on the propensity and prognostic score. Leacy and Stuart[10] explore this approach further in simulation studies, suggesting that treatment effect estimation is improved from the joint use of the propensity score and a prognostic score. Importantly, they find that methods which use both the propensity and the prognostic score still perform well when one of score models is incorrectly specified. This observation is reaffirmed by Antonelli et al.[9], who demonstrate that matching jointly on propensity and prognostic scores fit using a lasso model is doubly robust, meaning that the effect estimate from this approach is consistent as long as at least one of the score models is correctly specified.

However, in each of these studies, the prognostic model is fit on the entire control reserve. While this approach to creating the prognostic score seems effective, it would be desirable to fit the prognostic model on a held-out or historical set of controls in order to guarantee avoiding overfitting, as Hansen demonstrated was a risk.[22] In settings where there are many controls, a subset of the control sample could be left aside to fit the prognostic model. However, if this subset is held out at random, there’s no guarantee that the selected controls are nearby the treated observations in covariate space, so this approach runs the risk of extrapolating when fitting the prognostic score to the treated observations.

After establishing notation in section 2, we propose a method for fitting the prognostic score in section 3 to overcome the previously mentioned problems, then demonstrate through simulation a scenario in which this approach improves upon the results given by Mahalanobis distance matching and propensity score matching. Guidance is provided in considering the benefits and trade-offs the analyst faces in using this holdout design.

2 NOTATION AND BACKGROUND

We adopt the Neyman-Rubin potential outcomes framework, in which a sample is described by

\[ D = \{(X_i, T_i, Y_i)\}_{i=1}^{n}, \]

where individual \( i \) has covariates \( X_i \), treatment assignment \( T_i \), and potential outcomes function \( Y_i \). We will suppress the \( i \) index when context permits. We take \( T_i = 1 \) to represent that individual \( i \) was assigned to the treatment group and \( T_i = 0 \) to represent the control assignment. We define \( Y_i(T_i) \) to be the outcome of the individual under treatment assignment \( T_i \).

The fundamental challenge of causal inference is that we cannot observe both \( Y_i(0) \) and \( Y_i(1) \). Instead, we observe only one outcome, \( Y_i = T_iY_i(1) + (1 - T_i)Y_i(0) \). This makes it difficult to estimate \( E[Y(1) - Y(0)] \), the average treatment effect (ATE). In practice, it is also common to estimate the average treatment effect among the treated (ATT), since this is the quantity which most matching common methods attempt to estimate.
The propensity score is defined as \( e(X) = P(T = 1|X) \). Interest in the propensity score primarily stems from its use as a balancing score\(^{[11]}\), i.e.

\[ T \perp X \mid e(X). \tag{1} \]

That is, for level sets of propensity score, treatment assignment is independent of the measured covariates. Under the assumption of no unobserved confounding, and assuming that there is no possible value of the covariates \( X \) for which the probability of treatment is 0 or 1, balancing on the propensity score allows for the estimation of the treatment effect.

The prognostic score is defined by Hansen\(^{[7]}\) as any quantity \( \Psi(X) \) such that

\[ Y(0) \perp X \mid \Psi(X). \tag{2} \]

In particular, when \( Y(0)|X \) follows a generalized linear model, \( \Psi(X) = E[Y(0)|X] \). The prognostic score is, by definition, a balancing score. In other words, for level sets of the prognostic score, the potential outcome under the control assignment is independent of the observed covariates. Under the assumption that there is no unobserved confounding and that there is overlap between the treated and control groups for all values of \( \Psi(X) \), balancing by the prognostic score also allows for estimation of the treatment effect. The assumptions required to estimate the treatment effect by balancing on the propensity or prognostic score are slightly different, although we will not discuss them in completion here. (For a more thorough explanation, see Hansen\(^{[7]}\).)

### 2.1 Sensitivity to Unobserved Confounding

A study’s robustness to unobserved confounding is commonly assessed through analyses of \( \Gamma \) design sensitivity (discussed in detail by Rosenbaum\(^{[2,12]}\)). Such analyses suppose that assignments to treatment or control within an observational sample are actually determined in part by unmeasured confounding factors, and attempt to estimate what strength of unmeasured confounding would have to be present for the results of the study to come into question. In specific, we hypothesize that there is some unobserved confounding factor at play which causes certain individuals’ odds of treatment to be \( \Gamma \)-times greater than other individuals with the same observed baseline covariates. If \( \Gamma = 1 \), individuals with the same observed baseline covariates all have the same odds of treatment, as they would if we ran a randomized controlled experiment. Greater levels of \( \Gamma \geq 1 \) mean that, for individuals with the same observed baseline covariates, there is a greater departure in unobserved covariates which govern treatment assignment. The objective of a sensitivity analysis is to estimate the greatest possible value of \( \Gamma \) which could be at play before the conclusions of the study could change. Studies whose results would be reversed for \( \Gamma \approx 1 \) are considered extremely sensitive to imbalances in unobserved baseline covariates, whereas studies whose results would only be reversed in the presence of very large values of \( \Gamma \) would be considered more robust.

One important motivation for the importance of prognostic balance lies in the additional protection it provides against bias arising from unobserved covariates. Rosenbaum\(^{[2]}\) discusses the relative benefits from increasing the sample size of an observational study versus decreasing the heterogeneity of the sample. While both efforts will diminish the variance of the estimator, decreasing the unit heterogeneity of an observational study has the added effect of making the study more robust to larger levels of unobserved confounding (i.e. \( \Gamma \)). Intuitively, we imagine in our sensitivity analyses that we have some hidden adversary who, with a strength of \( \Gamma \), shifts the treatment probabilities of certain individuals in order to bias our results. If our matched individuals are wildly different in terms of their likely outcomes in the absence of treatment (i.e. large vertical distance in the Fisher-Mill plot in Figure 1), then our adversary has greater power to bias our results, even when \( \Gamma \) is small. Importantly, when this is the case, increasing the number of matched pairs we include will do nothing to improve our sensitivity to this bias. In contrast, when we select matched sets with individuals that are more similar in terms of their potential outcomes, our adversary can do less harm.

### 3 METHODS

#### 3.1 Motivation - The Pilot Design

Careful causal inference literature makes a distinction between the “design phase” and the “analysis phase” of a study\(^{[13]}\). During the design phase, all outcome data from the study is masked or unknown to the researcher, while important decisions about data collection, pre-processing, inclusion, and exclusion are made. Once the design phase is completed and locked in, the analysis phase begins. At this moment, the outcomes are revealed, and an estimation of causal effect is performed. This separation of design and analysis protects the integrity of the research by insulating the study design against any influence by the eventual
study results. In prospective randomized trials this separation is enforced by time. In observational studies, the researcher is responsible for enforcing the separation.

In the experimental setting, there is one case in which the researcher may be allowed to observe some outcome information during the design phase; this occurs when a pilot study is run. In this case, before running the experiment, researchers set aside a certain amount of their resources to conduct a smaller “pilot” study. The outcomes from the pilot study influence the subsequent study design, but the individuals in the pilot study are not reused in the final experiment, thereby upholding the separation between the design and analysis of the main experiment. Extending this metaphor to the observational setting, we propose the pilot design for the observational study. Using this approach, researchers may set aside a “pilot” sub-sample of their observations which are excluded from the final analysis so that they can be used to inform study design.

In this paper, we focus on using a pilot design to obtain prognostic information. That is, in order to select higher quality matches in the analysis data set, we examine how one might allocate a sub-sample of the data to fit a prognostic model which is then used to estimate prognostic scores for the rest of the study data. However, this is not the only potential use of the pilot design. For example, the pilot design may be useful when estimating an instrumental variable (analogous, for example, to when a pilot study is run to understand compliance behavior and recruitment for a larger RCT), or may be useful for model fitting when using an inverse weighting technique. When data are plentiful in an observational study, allocating these data “resources” towards improving the study design in such ways may prove more useful than reserving all data for the main analysis. Section 3.3 articulates a more specific suggestion for how this allocation may be done in the case of prognostic score matching.

3.2 Joint Matching and Fisher-Mill Plots

Once the prognostic model has been fit on the pilot data set and prognostic scores have been estimated for the remainder of the data, it is possible to match jointly on the prognostic score and the propensity score, as suggested by Hansen. Figure 1 visualizes the objective of this approach in a Fisher-Mill plot. We imagine a scenario in which each individual in our data set is represented in a reduced space of only two metrics: a measure of the covariates determining the expected treatment assignment ($\phi(X_i)$), and a measure of the covariates determining the expected outcome under control assignment ($\Psi(X_i)$). In this way, reducing variation in the horizontal direction equalizes the probability of treatment between compared individuals (emphasized by R. A. Fisher) while reducing variation in the vertical dimension equalizes the covariates important to the outcome (emphasized by J. S. Mill). These are the two features which are directly relevant to our matching: $\phi(X_i)$ balance (propensity balance) reduces bias, and $\Psi(X_i)$ balance (prognostic balance) reduces bias as well as variance and sensitivity to unobserved confounding.

Optimal Mahalanobis distance matching (Figure 1A), pairs individuals who are closest in the full covariate space. However, since not all covariates are important for prognosis or treatment assignment, individuals who are close in the full covariate space may be relatively distant when considered in terms of $\phi(X_i)$ and $\Psi(X_i)$. Propensity score matching (Figure 1B) aims to pair individuals who are close in the covariates important for treatment assignment, $\phi(X_i)$, but not for prognosis, $\Psi(X_i)$. This matching will reduce bias in the estimation of causal effect compared to the unmatched data set, but will lose much of the protection from variance and unobserved confounding conferred by prognostic balance. In contrast, matching jointly on $\phi(X_i)$ and $\Psi(X_i)$, seeks to pair individuals who are close together in the reduced feature space. This optimizes for both desirable types of covariate balance: prognostic and propensity.

3.3 Prognostic Pilot Matching

We propose the following pilot matching design for constructing and applying the prognostic score in the study design phase (Algorithm 1). The main steps are:

1. Fit a propensity model $\hat{\phi}$ on the entire data set, $D$.
2. Separate the data into a held-aside “pilot” sample $P$ and an analysis sample, $D'$
3. Fit a prognostic score model $\hat{\Psi}$ using outcome information from only $P$.
4. Perform Mahalanobis distance matching on $D'$ based on the prognostic and propensity scores estimated from $\hat{\phi}$ and $\hat{\Psi}$.

1Note: other dimensions — such as one for instrumental variables, or one for expected treatment outcome under treatment — might be included as useful extensions to these plots
A “Fisher-Mill plot.” The horizontal axis, $\phi(x)$, shows variation important for determining treatment assignment (log-propensity score), while the vertical axis, $\Psi(x)$, shows variation important for determining the outcome in the absence of treatment (prognostic score). Blue dots represent control individuals, red dots represent treated individuals, and dotted lines connect matched pairs. Each plot shows optimal 1:1 matches of a simulated data set based on Mahalanobis distance in the whole covariate space (A), true propensity score (B), and Mahalanobis distance in the feature-reduced space of true propensity score and true prognostic score (C). The data set was generated according to the simulation set up in section 4.2 with $\rho = 0.5$.

One method for doing so is suggested in Algorithm 1. In this approach, the pilot set is selected by first constructing a 1:2 Mahalanobis distance matching of each treated individual (denoted $A_1, \ldots, A_{n_T}$, where $n_T$ denotes the number of treated individuals) to a set of two control individuals (denoted $B_1, \ldots, B_{n_T}$). Then from each pair of matched controls ($B_i$), we select one individual at random ($b_i$) to place into our pilot set. This gives a pilot set, $P$ of size $n_T$, which is used to estimate the prognostic model and then removed from the analysis. The preliminary 1:2 Mahalanobis distance matching ensures (1) that the individuals in the prognostic set are relatively close in the covariate space to the treated individuals, minimizing extrapolation of $\hat{\Psi}$, and (2) that not all individuals close in the covariate space to the treated individuals are removed from $D'$, because this might sacrifice too many potentially high-quality matches.

**Algorithm 1** Prognostic Pilot Matching

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**Input:** $D = \{(X_i, T_i, Y_i)\}_{i=1}^n$, fixed treated to control ratio $k$.

1. Fit a linear propensity model $\hat{\phi}$ using $D$.
2. Construct a 1 : 2 Mahalanobis distance matching $(A_1, \ldots, A_{n_T}; B_1, \ldots, B_{n_T})$.
3. For $i \leftarrow 1$ to $n_T$ do
   - $b_i \leftarrow$ a control chosen uniformly at random from $B_i$.
4. $P \leftarrow \{b_i\}_{i=1}^{n_T}$
5. $D' \leftarrow D \cap P^C$
6. Fit a linear prognostic model $\hat{\Psi}$ using held out controls $P$.

**Output:** 1 : $k$ Mahalanobis distance matching of $D'$ using $\hat{\phi}$ and $\hat{\Psi}$.

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There are several alternative approaches to carry out steps 1-4; we do not intend to prescribe a single method for doing so. For example, at steps (1) and (3), a researcher may select from any number of models to fit. In cases where the covariate space is especially large, sparsifying models such as the lasso may be appropriate (this is considered extensively by Antonelli et al[3]). In step (4), the researcher may choose between pair matching, 1:k matching (for example, in Figure 1), full matching (Figure 4), or some other sub-classification method.
Finally, we must consider other reasonable methods to separate the pilot and analysis data sets in step (2). For example, systematically selecting the lower quality match from the set of matched controls might ensure that high quality matches to the treated individuals are left behind for the analysis set. When data are especially plentiful or the prognostic model is especially elusive, one might perform a preliminary matching of 1:4 or more (rather than 1:2) and select more than a single control individual from each matched set to allocate more data to the pilot set. If the sample is so large that a preliminary Mahalanobis distance matching on the entire data set would be too computationally taxing, the pilot set might be selected at random, either uniformly or while stratifying by important covariates (e.g., sex, smoking status, age group). Each of these decisions should ultimately be made based on the specific data set and research question at hand.

3.4 Mathematical Results

In this section we include motivating mathematical results supporting the joint usage of propensity and prognostic score information in matching. First, as an illustrative example, we give forms of the bias, variance, and MSE of a simple pairmatching effect estimator in terms of the prognostic score. Second, we review and extend the results of Antonelli et al.9, to give the asymptotic consistency of the pilot matching estimator. In particular, we note that asymptotic consistency is achieved as long as at least one of two models (for propensity and prognostic score) is correctly specified. This implies that pilot matching designs are doubly robust.

3.4.1 Properties of a simple matching estimator in terms of prognosis

Suppose we observe \( n_T \) treated individuals (indexed by \( i \)) and we match each one to exactly one control individual. For each \( i \), let \( j(i) \) represent the index of the control individual matched to the \( i \)-th treated individual.

Suppose we additionally assume the following:

1. \( Y(0) = \Psi(X) + \epsilon, \) where \( \epsilon \sim \text{i.i.d.} \, N(0, \sigma^2) \)
2. \( \epsilon \) is independent of \( X \) and \( Y \)
3. The differences in outcomes between matched pairs, \( D_i = Y_i - Y_{j(i)} \), are independent.

**Theorem 1.** Assume the statements above and suppose \( \tau \) is a constant additive treatment effect. If we estimate the ATT via \( \hat{\tau} = \frac{1}{n_T} \sum_{i=1}^{n_T} D_i \), then

\[
\text{Var}(\hat{\tau}) = \frac{4\sigma^2}{n_T} + \frac{1}{n_T} \text{Var}\left(\Psi(X_i) - \Psi(X_{j(i)})\right),
\]

(3)

\[
\text{Bias}(\hat{\tau}) = E\left[\Psi(X_i) - \Psi(X_{j(i)})\right],
\]

(4)

and

\[
\text{MSE}(\hat{\tau}) = \frac{4\sigma^2}{n_T} + \frac{1}{n_T} \text{Var}\left(\Psi(X_i) - \Psi(X_{j(i)})\right) + \left(E\left[\Psi(X_i) - \Psi(X_{j(i)})\right]\right)^2
\]

(5)

\[
\leq \frac{4\sigma^2}{n_T} + E\left[\left(\Psi(X_i) - \Psi(X_{j(i)})\right)^2\right]
\]

(6)

Moreover, if assumptions 2 and 3 do not hold, the right hand side of (1) and (3) become upper bounds, and (2) and (4) still hold.

Theorem 1 expresses the bias, variance, and MSE of a simple matching estimator in terms of the prognostic score. A derivation is supplied in the Appendix. In particular, we find that the variance in the matching estimator is bounded by the variance in the difference between the prognostic scores. This means that the variance in estimation can be decreased even if the difference in prognostic score within matched pairs is large, as long as this difference in score is relatively constant across all matched pairs. Equation (4), however, implies that a large mean difference in prognostic score within pairs will increase the bias of the estimator, even if the variance is not affected. These results combine to give equation (5), which reiterates how minimizing both the mean difference and the variance in the difference in prognostic scores across matched pairs gives a reduction in MSE. Finally, (6) shows how the MSE of the estimator can be bounded by the mean squared variation in prognostic score between matched pairs (although this bound is fairly loose).
3.4.2 Doubly Robust Pilot Matching

Theorem 1 from Antonelli et al.\(^9\) shows that the average treatment effect is identifiable when conditioning jointly on the propensity and prognostic score. In specific, this identifiability holds as long as at least one of the two score models is correctly specified. This helps to explain the simulation results of Leacy and Stuart\(^10\), in which matching methods which used the propensity and prognostic score jointly performed well even when one model was incorrectly specified.

In 2005, Bang and Robins\(^14\) introduced a notion of “doubly robust” estimation. This term has come to refer to any estimator which combines an outcome model with a model for the probability of treatment in such a way that the estimator is consistent or “correct” as long as at least one of the models is correctly specified. Antonelli et al.\(^9\) propose a doubly robust matching estimator (DRME), which uses a lasso regression to estimate \(\hat{\phi}\) and \(\hat{\psi}\). Theorem 2 of this report shows that the lasso estimator is indeed consistent under suitable regularity conditions, provided at least one of the models is correctly specified. Here, we state a slightly more generalized version of that theorem which allows for a more broad class of doubly robust matching designs in which \(\hat{\phi}\) and \(\hat{\psi}\) can be estimated by methods other than the lasso. In this form of the theorem, we clarify how the rate of convergence for the estimator from the pilot design depends on: (1) the sample size of the pilot data set (2) the sample size of the analysis data set, and (3) the specific method selected to fit \(\hat{\phi}\) and \(\hat{\psi}\).

Let \(n_{y}\) and \(n_{p}\) be the sample sizes of the analysis and the pilot data sets, respectively. Following the notation of Antonelli et al.\(^9\), let \(\hat{\theta}\) represent a vector of the estimated parameters for the propensity and prognostic models (\(\hat{\phi}\) and \(\hat{\psi}\)), and, for a given \(\hat{\theta}\), let \(Z = (\hat{\phi}(X), \hat{\psi}(X))\). In keeping with Abadie and Imbens\(^5\) and Antonelli et al.\(^9\), suppose the \(M\) matches for the \(i^{th}\) individual with score model parameters \(\theta\) are given by

\[
J_M(i, \theta) = \left\{ j = 1, \ldots, n_{y} : T_j = 1 - T_i, \left( \sum_{k : T_k = 1 - T_i} I(\|Z_i - Z_k\| \leq k) \right) \right\},
\]

(7)

Where \(I\) is an indicator variable and \(\|\cdot\|\) is some distance measure; in most cases Mahalanobis distance. Note that this is slightly different than the matching scheme used in this simulation study and in many study designs, in that each individual (both treated and control) is matched with the \(M\) nearest individuals of the opposite treatment assignment in the analysis set, and individuals may be used more than once. In practice, many studies use matching without replacement, which we consider here in simulation.

Finally, let \(\tau(\theta)\) represent the estimator obtained from the matching given by \(J_M(i, \theta)\):

\[
\tau(\theta) = \frac{1}{n_{y}} \sum_{i=1}^{n_{y}} \left( 2T_i - 1 \right) \left( Y_i - \frac{1}{k} \sum_{j \in J_M(i, \theta)} Y_j \right).
\]

(8)

**Theorem 2.** (Generalization of Antonelli et al.\(^5\)) Suppose that \(\hat{\theta}\) is estimated on the pilot data set by some method such that \(\hat{\theta}\) converges to its probabilistic limit \(\hat{\theta}\) at a rate \(R(n_{p})\). Under regularity conditions described in the appendix (including no effect modification), and assuming that at least one of the models for propensity or prognosis is correctly specified, then,

\[
\tau - \tau(\hat{\theta}) = O_p \left( \frac{1}{n_{y}} \right) + o_p \left( R(n_{p}) \right)
\]

(9)

If both \(n_{p}\) and \(n_{y}\) are allowed to go to infinity as the sample size increases, and if \(R(n_{p})\) is bounded as \(n_{p} \rightarrow \infty\), then we have that \(\tau(\hat{\theta})\) is a consistent estimator for \(\tau\).

This result is almost immediate from the proof for theorem 2 in Antonelli et al.\(^2\); however a more specific explanation can be found in the appendix.

An explanation for the notation used in this theorem can be found in Van Der Vaart\(^14\). Intuitively, the first term on the right hand side of (10) describes how the error in estimation depends on the sample size of the analysis set: As the size of the analysis set increases, the number and quality of matches will increase, allowing for better estimation. The second term on the right hand side describes how the error depends on the sample size of the pilot set: As the sample size of the pilot set increases, we will fit more accurate models for propensity and prognosis, allowing us to identify the higher quality matches from the analysis set.

This form of the theorem provides for doubly robust matching estimation from a pilot matching design, provided any suitable choice of method for estimating \(\hat{\theta}\). Additionally, it is important to note that the sample sizes of both the pilot data set and the analysis data set must go to infinity for consistency, yet the choice of the specific method used to partition the pilot and analysis
data sets can be left to the researcher. A deeper discussion of the design choices for the pilot matching procedure can be found in.

4 | SIMULATIONS

4.1 | Objective

Any approach which specifically removes observations from the analysis phase involves several design considerations. We specifically highlight four, often interacting, considerations when selecting a pilot matching design or similar approach:

1. Correlation of treatment and prognosis (5.3.1) - if the treatment and the outcome are tightly correlated, matching on the propensity score may provide some prognostic balance as well. Prognostic score balancing methods may be especially helpful if there is a lot of variation in covariates which are important to the outcome but unrelated to treatment assignment.

2. Trade offs in sample size (5.3.2) - allocating data for use in the design phase decreases the amount of data available in the analysis phase.

3. Trade offs in match quality (5.3.3) - when overlap between the treatment and control groups is poor, care must be taken in allocating data to the analysis and pilot sets.

4. Fitting the propensity and prognostic models (5.3.4) - if the data generating process for treatment assignment and outcome is particularly hard to model, this may influence the usefulness of methods which rely on fitted scores.

We performed a simulation study to assess the performance of pilot matching compared to Mahalanobis distance and propensity score matching and investigate the four design considerations above. The following subsection describes the data-generating process used in our simulations, and section 5 gives the results.

4.2 | Setup

We compare the performance of propensity score matching, Mahalanobis distance matching, and pilot matching (described in section 3.3) on simulated data while varying the fixed control to treatment ratio (k) used in the matching and the correlation between the true propensity and prognostic score (ρ, below). Suppose we measure p covariates, so that \( X \) is a p-dimensional vector. Let \( I_p \) denote the \( p \times p \) identity matrix. The generative model for our main set of simulations is the following:

\[
X_i \overset{i.i.d.}{\sim} \text{Normal}(0, I_p), \\
T_i \overset{i.i.d.}{\sim} \text{Bernoulli} \left( \frac{1}{1 + \exp(-\phi(X_i))} \right), \\
Y_i = \tau T_i + \Psi(X_i) + \epsilon_i, \\
\epsilon_i \overset{i.i.d.}{\sim} \text{N}(0, \sigma^2),
\]

where the true propensity and prognostic scores are given by the linear combinations

\[
\phi(X_i) = X_{i1}/3 - c, \\
\Psi(X_i) = \rho X_{i1} + \sqrt{(1 - \rho^2)}X_{i2}.
\]

Importantly, these values ensure that \( \rho \) is precisely the correlation between \( \phi \) and \( \Psi \) (i.e. Cor(\( \phi(X_i) \), \( \Psi(X_i) \)) = \( \rho \)). When \( \rho = 0 \), the treatment effect is completely unconfounded, since treatment assignments are entirely determined (up to randomness) by variation in \( X_{i1} \), and outcome (under the control assignment) is entirely determined by variation in \( X_{i2} \). When \( \rho = 1 \), the problem is highly confounded, since outcome and treatment assignment are both determined solely by variation in \( X_{i1} \).

We fix the treatment effect to be constant with \( \tau = 1 \), the number of covariates \( p = 10 \), and the noise in the outcomes \( \sigma = 1 \). Each simulation consisted of a data set of total sample size \( n = 2000 \), and simulations were repeated \( N = 1000 \) times. The
constant, $c$, in the propensity score formula was chosen such that there were approximately 100 treated observations in each data set (e.g. for a sample size of 2000, the value $c = 3$ was used). We consider $1:k$ matchings of the analysis set for $k = 1, \ldots, 10$, and $p = 0, 0.1, \ldots, 0.9, 1.0$. In simulated samples, the Cohen’s D standardized difference between the outcomes of the treated and control groups was approximately 0.6 to 1.0 (depending on the value of $p$).

In order to understand the influence of other factors, we ran additional simulations which kept all other parameters as listed above except:

- The number of covariates was increased from $p = 10$ to $p = 50$.
- The sample size was decreased from $n = 2000$ to $n = 1600$. (In this case, $c$ was changed to 2.75 to keep the number of treated individuals consistent.)
- The noise in the outcome was increased from $\sigma = 1$ to $\sigma = 2$.
- Instead of performing $1:k$ matching in the final step, full matching was used. As in the $1:k$ matching, the full match was based on Mahalanobis distance in the combined space of $\hat{\Phi}$ and $\Psi$. In this case, $N = 2000$ simulations were performed to get accurate assessments of performance.

When using $1:k$ matching, we estimate ATT and design sensitivity $\Gamma$ using the permutation $t$-statistic from the package `sensitivityvmd`. When using full matching, we estimate ATT using the package `sensitivityfull`. The accuracy of each matching method was assessed based on the empirical bias, standard deviation, and mean squared error (MSE) of the estimates produced in simulation. Design sensitivity was assessed in terms of the median $\Gamma$ design sensitivity. All matching assignments were found using `optmatch`, which makes use of the RELAX-IV algorithm. Source code and data files for these simulations are publically available on github (https://github.com/raikens1/PilotMatch).

5 | RESULTS

5.1 | Primary Simulations

We first consider the main simulation set-up described in section 4.2. In this case, there are approximately 19 control individuals observed for every one treated individual. Figure 2 shows the bias and variance of $1:k$ matching for each method.

First, we observe that the bias from Mahalanobis distance matching is large, and it increases with the correlation between prognosis and treatment assignment (Figure 1A). It is unsurprising that bias increases as $p$ approaches 1, since this means the treatment assignments are highly correlated with the potential outcomes. Mahalanobis distance suffers the most, probably because there are only two covariates, $X_1$ and $X_2$, which are actually important to treatment assignment or outcome, yet this method equally weights $X_1$ alongside 8 other covariates which are entirely random noise unimportant to the problem. In further simulations, we find that this issue is exacerbated when the number of uninformative covariates is increased (Supplementary Figure 1).

Figure 2B demonstrates how pilot matching may actually decrease the variance in the estimator under the right conditions, in spite of the fact that it reduces the size of the sample which may be used for estimation. Propensity score matching has highest standard deviation, and this is worse when $p$ is close to zero. This is because, when $p$ is small, the propensity score contains no information about prognosis under the control assignment. This causes the propensity score method to match observations which may be very different in terms of their potential outcome under the control assignment, giving poor prognostic balance and thus larger variance in the estimate of the causal effect. While Mahalanobis distance performs slightly better, it is again choosing lower quality matches because of the uninformative covariates in the data. The lowest variance is achieved by pilot matching, since this algorithm optimizes for prognostic balance as well as propensity score balance.

Figure 3 shows the mean squared error and median gamma sensitivity from the same set of simulations as in Figure 2. In Figure 3A, pilot matching does comparatively well compared to the other two methods in terms of mean squared error, because of the protection against bias and variance shown in Figure 2.

A unique potential benefit of pilot matching designs, however, is the increased robustness to unobserved confounding (Figure 3B). Propensity score matching gives the lowest $\Gamma$ values (i.e. most sensitivity to unobserved confounding), especially when $p$ is small. When $p$ is close to zero, the propensity score captures little prognostically relevant variation in the baseline covariates, so the matches produced have poor prognostic balance. As $p$ increases, the prognostic score and the propensity score become
highly correlated, so matching on propensity score starts to give some prognostic balance as well as propensity balance. While the Gamma sentitivity of Mahalanobis distance matching seems promising when \( \rho \) is large, most of this is likely due to the large amount of bias in the effect estimate from this method (Figure 2A). By matching using \( \Psi \), pilot matching directly optimizes for prognostic balance in the matched sets. Thus the pilot method has better protection against unobserved confounding, without giving a highly biased estimator.

5.2 Full Matching

The primary simulation results above are concerned with matching a single treated individual to a fixed number, \( k \), of control individuals in the analysis set, since this method is the most common. However, once the prognostic score is built from the pilot data set, the researcher may choose from any number of methods to subclassify or match the analysis set based jointly on the prognostic and propensity scores. As an illustration, we completed an additional batch of simulations in which the analysis set was subclassified using full matching. This method represents a more flexible alternative to fixed \( 1:k \) matching, in which the ratio of treated to control individuals is allowed to vary within each matched ‘set.’ It is similar in spirit to the ‘variable-ratio’ matching applied by Pimentel et al. In essence, treated individuals which are similar to many control individuals, whereas treated individuals which are similar to few control individuals are matched with few control individuals (see Hansen or Stuart and Green for applied examples). In this way, full matching uses all of the observations in the analysis data set exactly once while often selecting closer matches than fixed \( 1:k \) matching.

Figure 4 shows the bias (A), variance (B), and MSE (C) of full matching using Mahalanobis distance matching, propensity score matching, and matching jointly on the propensity and prognosis (‘pilot full matching’). We find that full matching using propensity and pilot full matching yield comparable or superior performance compared with \( 1:k \) matching with a well-selected \( k \). Additionally, we find in our simulations that pilot full matching tends to outperform full matching on just the propensity
FIGURE 3 Mahalanobis, propensity, and pilot matching performance in terms of MSE (A) and Gamma Sensitivity (B) for 1:k optimal matching as the correlation between propensity for treatment and prognosis, $\rho$ varies from 0 to 1.

FIGURE 4 Performance from full matching based on Mahalanobis distance, propensity score and pilot matching.

score. These results suggest that full matching jointly on propensity and a prognostic score from a held-aside ‘pilot’ sample may present a promising design strategy for some observational studies.
5.3 | Methodological Considerations

The simulations discussed in the previous section illustrate a use case in which pilot matching is particularly useful: There is an abundance of control individuals which overlap fairly well with the treated population, and the underlying processes dictating propensity and prognosis are easily fit with standard linear models (although both propensity and prognostic models are overspecified). In this section, we discuss four design considerations which are important to the selection of the study design:

1. Correlation of treatment and prognosis (5.3.1)
2. Trade-offs in sample size (5.3.2)
3. Trade-offs in match quality (5.3.3)
4. Fitting the propensity and prognostic models (5.3.4)

5.3.1 | Correlation of Treatment and Prognosis

A first consideration is the correlation, \( \rho \), between the variation, \( \phi(X_i) \), important for determining the treatment assignment, and the variation, \( \Psi(X_i) \), important for determining the outcome in the absence of treatment. Figures 2 and 3 show the performance of each matching method as \( \rho \) varies from 0 to 1. When the correlation is close to one, only one covariate, \( X_{i1} \), is important for both treatment assignment and potential outcome under the control assignment. When this happens, all methods unsurprisingly reach their greatest levels of bias (Figure 2A). Mahalanobis distance matching suffers the worst from this phenomenon because it is matching on several covariates which are unimportant to either treatment assignment or outcome.

One result of interest is that propensity score matching estimator achieves its lowest variance when confounding is worst. This is because, when propensity and prognosis are highly correlated, matching on the covariates most important for treatment assignment also imposes balance in the covariates most important for prognosis. This prognostic balance, reduces the variance (Figure 2B) and increases robustness to confounding (Figure 3B).

In contrast, when treatment assignment is less closely correlated with potential outcome, propensity score matching suffers most from high variance in the effect estimate (Figure 2B), because it is blinded to the covariates important for determining the outcome under the absence of treatment. This means that ideal propensity score matches may be quite distant in terms of the prognostic score (Figure 1B). These are the scenarios in which pilot matching is most protective against variance in estimation, since it seeks to optimize for prognostic balance as well as propensity balance on the matched sets.

5.3.2 | Trade-offs in Sample Size

A second consideration is the trade-off in control sample size implicit in creating a held-asideset for fitting the prognostic score prior to matching. In the pilot algorithm, one control individual for each treated observation is removed from the analysis data set for the purpose of fitting the prognostic score. In our simulations, this amounts to a sacrifice of \( \sim 100 \) observations.

In general, increasing the sample size of a matching study has two main goals: (1) to decrease the bias of the estimator by enabling higher quality matches, and (2) to decrease the variance of the estimator by matching more individuals (e.g. increasing \( k \) in \( 1 : k \) matching). We discuss the latter point here, and the former in section 5.3.3.

Roughly speaking, the square root law implies that the standard error of the sample mean tends to decrease at the rate \( \frac{1}{\sqrt{n}} \), where \( n \) is the sample size. This means that increasing the number of observations used in the analysis phase of the study decreases the variance of effect estimation, but with diminishing returns. This is especially true because, in fixed-ratio matchings of large samples, it is already common to discard many control individuals simply because they are poor matches to all individuals in the treatment group. Thus, if the sample size is already quite large, retaining, say, an additional 100 control individuals for the analysis set will yield only a very small reduction in the variance of the effect estimator.

In contrast, increasing the number of observations used in the pilot data set increases the researcher’s ability to achieve prognostic balance in the analysis data set, which has a variance-reducing effect (Figure 2B). This means that when the control reserve is very large, it may in fact be variance-reducing to “sacrifice” some individuals from the analysis set so that the overall matched sets compared in the analysis phase have better prognostic balance. This trade-off, of course, depends on the total size of the control reserve. This is illustrated in Figure 4. Since full matching uses all of the treated and control individuals, the pilot full match has approximately 100 fewer control individuals to use for estimation than the alternative methods. However, in these simulations, the variance of the estimator from pilot full matching is actually smaller than that for the other methods (Figure 4).
5.3.3 | Trade-offs in Match Quality

**FIGURE 5** Mahalanobis, propensity, and pilot matching performance in terms of Bias (A), Variance (B), and MSE (C) for 1:k optimal matching with a smaller control reserve (n = 1600).

In some observational data sets, there may be many observations total but few individuals who are readily comparable between the treatment and control groups. In a Fisher-Mill plot, we might visualize this as point clouds for treatment and control groups with very little overlap. When this occurs, there may be an abundance of “low-quality” controls which are very dissimilar from the treatment group, and a paucity of precious “high-quality” controls. In pilot designs (even those which do not specifically carry out joint matching on prognosis and propensity), the allocation of these high quality controls is a difficult problem. When fitting the prognostic score, for example, it is desirable to use controls which are close to the treated individuals in order to minimize the amount of extrapolation necessary to estimate prognostic scores for the treatment group. However, these individuals are also the best matches to the treatment group for the purposes of obtaining the final effect estimate.

In the pilot matching algorithm given in 3.3, we use a preliminary Mahalanobis distance matching to select controls for the pilot data set which are nearby to the treated individuals in the covariate space. However, depending on the nature of the data collected, allocating these observations to the pilot set can force the subsequent matching efforts to compromise on lower quality matches, increasing bias and - in some cases - variance (Supplementary Figure 2). This effect is most pronounced when (A) 1 : k matching is performed and k is large, (B) the control reserve is small, or (C) overlap of the treated and control individuals is poor.
(Figure 2A, Figure 5A, Supplementary Figure 2). When \( k \) is large, bias for all methods is worse because lower quality matches are being carried over to the analysis phase. If the control reserve is small and/or there is little overlap between the treated and control individuals, every control individual which is close in covariate space to the treated individuals is a precious potential match, and sacrificing these individuals means that there are fewer good alternatives to choose from. Additionally, we find that poor overlap combined with high large \( \rho \) tends to increase the variance of the estimator for both pilot matching and propensity score matching (Supplementary Figure 2), especially when \( k \) is large. We hypothesize that this is because both methods are forced to chose matches which are more distant both in propensity and prognostic score. In particular, this prognostic imbalance induces increased variance in estimation.

As a result, we advise the following: First, one approach to keep bias low while maximizing data usage is to use a matching method on the analysis set that allows for variable ratios of treatment to control individuals across subclasses, such as full matching or variable-ratio matching, described in 5.2. Second, just as with the selection of \( k \), the choice to use pilot matching and the method to select the held-out set should depend on the data. Because of the sacrifice in match quality associated with discarding some individuals, pilot matching is most appropriate when the control reserve is plentiful, particularly in the region of overlap between treated and control individuals.

### 5.3.4 Fitting the Propensity and Prognostic Models

Our final consideration is that of fitting the propensity and prognostic models themselves. This simulation was largely a proof of concept, with the true data generating processes for treatment assignment and prognosis fairly simple and easily fit by common linear modeling methodologies. In practice, the researcher may choose to draw from whatever model fitting methodologies they prefer to capture the prognostic score.

**FIGURE 6** Empirical 1:1 matches based on Mahalanobis distance in the whole covariate space (A), estimated propensity score (B), and pilot matching (C). Blue dots represent control individuals, red dots represent treated individuals, and dotted lines connect matched pairs. Data was simulated according to the set up in section 4.2 with \( \rho = 0.5 \).

It is intuitive that the value of pilot matching is greatest when the propensity and prognostic score models are most accurate. In contrast to figure 1, which shows the idealized matches that would be selected if the propensity and prognostic scores were precisely known, figure 6 displays the matches which might be selected in practice based on estimated score models. It is important to note that both propensity and pilot matching rely on effective modeling of propensity and/or prognostic scores; in cases where the model is imperfect, imperfect matches will be selected. In fact, in simulations where more random variation is added to the outcome, we find that the performance of pilot matching is diminished because the prognostic score is harder to fit (Supplementary Figure 3). In cases like these, it may be useful to budget more data for fitting the prognostic score (if able), or to use more sophisticated modeling techniques. When the control reserve is particularly abundant, this may be an opportunity to leverage more data for the purpose of building a very accurate model for prognosis to be used in matching.
One additional consideration is that the researcher sometimes has intuition *a priori* about whether the propensity or the prognostic score will be harder to fit. For example, when the outcome is continuous and the treatment is binary, the continuous outcome may be easier to model. In this case, the researcher might favor prognostic score matching, or might give different weight to the prognostic and propensity score in the matching process.

6 | CONCLUSIONS

Reducing the number of observations used in inference seems a peculiar design choice. But the primary intuition is straightforward: use resources to gain information on how to plan a stronger study design. What perhaps defies traditional intuitions is that pilot matching, through using observational units in the design phase rather than the analysis phase, can improve robustness to challenges arising from unobserved covariates.

Modern observational studies benefit from having access to sample sizes that are unparalleled by randomized controlled trials. But they suffer from bias arising from non-random assignment. Particularly problematic are imbalances in pre-treatment covariates that are unobserved. Unfortunately, there is no guarantee that including more observational units in the analysis phase will produce less biased results. In fact, uncertainty measures like confidence intervals are particularly deceptive because they are incapable of measuring uncertainty due to potential unobserved covariate imbalances. Great care must be given to strategies to minimize the potential impact of both observed and unobserved imbalances in the covariates.

Pilot matching aims to emulate a two-phase, prospective randomized trial design. In a prospective study, the analyst has fixed resources to achieve a strong study design. Blocking on prognostically important covariates and randomizing within these blocks yields efficient studies. But where does the information on the most prognostically important covariates come from? Sometimes we can use expert knowledge, but often this information is derived from careful pilot studies. If resources permit, then the researcher can allocate some of these resources to run a pilot study in order to observe valuable correlations which can be put to use in constructing the blocks in the full study.

Because pilot matching is deployed in observational study designs, using pilot matching with the objective of minimizing the within matched set differences in the prognostic score yields an additional benefit which is not analogous to anything encountered in prospective randomized trial design. As demonstrated by Rosenbaum, and underscored here, constructing matched sets which are quite close on their prognostic score tend to produce study designs which are more resistant to having their conclusions explained away by confounding arising from imbalances in unobserved covariates. Another benefit of pilot matching, not explored in this paper, is technical in nature: Though optimal matching is excellent at creating sets with minimal within set differences, the algorithms’ runtimes do not scale well in the number of observations. Generally, creating continuous prognostic and propensity scores simplifies the creation of subsets of quite similar observations for distributed computing.

In modern observational studies, both the number of observations and the number of covariates tend to be large. The benefit of pilot matching is to reduce the dimensionality of the problem; describing the match quality in the principal dimensions of prognosis and treatment assignment. The use of Fisher-Mill plots helps to visualize the distributional issues inherent in these types of matching problems.

In section 5.3, this study explored four trade-offs faced by the researcher in designing an observational study using pilot matching. Though we made the choice to motivate this paper in the large control reserve setting, in the simulations it becomes apparent that pilot matching may also be quite useful when the number of observations is large but only 1:1 matching is achievable.

Future work on selecting the pilot set, assessing the benefit when different levels of correlation between the prognostic score and propensity scores exist, as well as clever modeling choices for fitting the scores will be beneficial. A small, but useful, extension to the Fisher-Mill plot is to include additional dimensions that describe (i) the conditionally independent variation in the encouragement to treatment (e.g., a measurement of the instrumental variable assignment) when considering the formation of matched sets, and (ii) the estimated outcome for individual units under treatment - which will be particularly helpful in settings with heterogeneous treatment response.

ACKNOWLEDGMENTS

The authors would like to thank Jonathan H. Chen for contributing his computational resources to this project. RCA is supported by funding from the National Institutes of Health (T32 LM012409) and a Stanford Graduate Fellowship in Science and Engineering. DG is supported internally by the Stanford Department of Statistics.
Author contributions
All authors contributed to the design and set-up of the simulations and the development of the pilot matching method. RCA and DG developed the code, ran the simulations, and generated the figures. RCA developed the mathematical results. RCA, DG, and MB wrote the manuscript. All authors contributed to the editing and revision of the manuscript.

Financial disclosure
None reported.

Conflict of interest
The authors declare no potential conflict of interests.

SUPPORTING INFORMATION

The following supporting information is available as part of the online article:
Figure S1. Bias and standard deviation of estimation when the number of covariates is increased to 50
Figure S2. Standard deviation of effect estimation when the overlap between treated and control individuals is diminished.
Figure S3. MSE and median gamma design sensitivity of effect estimation when the random noise contributing to the outcome is increased.

How to cite this article: R. Aikens, D. Greaves, and M. Baiocchi (2019), Using the Prognostic Score to Reduce Heterogeneity in Observational Studies, , 2019;XX:Y–Z.

APPENDIX

A PROOF OF THEOREM 1

Proof of Theorem 1. We will first derive the result for variance.

\[ V_\text{ar}(\hat{\tau}) = \frac{1}{n_T} V_\text{ar}(D_i) \]
\[ = \frac{1}{n_T} V_\text{ar}(Y_i - Y_{j_0}) \]
\[ = \frac{1}{n_T} V_\text{ar}(\tau + Y_{i}(0) - Y_{j_0}(0)) \]
\[ = \frac{1}{n_T} V_\text{ar}(\Psi(X_i) + \epsilon_i - \Psi(X_{j_0}) - \epsilon_{j_0}) \]
\[ = \frac{4\sigma^2}{n_T} + \frac{1}{n_T} V_\text{ar}(\Psi(X_i) - \Psi(X_{j_0})) \]

If assumption 3 is false then the statement becomes an inequality at line 5. If assumption 3 is false then the statement becomes an inequality at lines 1-5.

Next, bias:
Bias(\hat{\tau}) = E[D_i - \tau] \\
= E[Y_i(0) + \tau - Y_{j(0)}(0) - \tau] \\
= E[Y_i(0) - Y_{j(0)}(0)] \\
= E[\Psi(X_i) + e_i - \Psi(X_{j(0)}) - e_{j(0)}] \\
= E[\Psi(X_i) - \Psi(X_{j(0)})]

Thus, for the MSE we have

\[
MSE(\hat{\tau}) = \frac{4\sigma^2}{n_T} + \frac{1}{n_T} Var(\Psi(X_i) - \Psi(X_{j(0)})) + \left(E[\Psi(X_i) - \Psi(X_{j(0)})]\right)^2 \\
\leq \frac{4\sigma^2}{n_T} + E\left[(\Psi(X_i) - \Psi(X_{j(0)}))^2\right]
\]

B NOTES ON THEOREM 2

B.1 Conditions Necessary for Theorem 2

In keeping with Antonelli et al., let $D_{ij} = \|Z_j(\theta) - Z_i(\theta)\|^2$, and let $D_{ik}$ represent the k-th order statistic of $\{D_{ij} = \|Z_j(\theta) - Z_i(\theta)\|^2 : T_j = 1 - T_i\}$ for a fixed $i$. Additionally let $f_{D_{j\theta}}$ represent the probability density function of $D_{ij}$ for a fixed $i$ and $\theta$. Let $C_{iM} = \frac{D_{iM+1} + D_{iM+2}}{2}$, and let $l_{ij}(\theta) = C_{iM} - \|Z_j(\theta) - Z_i(\theta)\|^2$. Last, let $H_{ij}(\theta) = Y^2_i Y^2_j \left(\frac{\partial}{\partial \theta} l_{ij}(\theta)\right)^2 \left(\frac{\partial}{\partial \theta} \frac{\partial}{\partial \theta} l_{ij}(\theta)\right)$

Theorem 2 requires the following:

1. SUTVA, strong ignorability, positivity
2. No effect modification
3. At least 1 of the 2 models for propensity or prognosis is correctly specified
4. $\int f^2_{D_{j\theta}}(x)dx < \infty$ and $\int f^2_{D_{j\theta}}(x)dx < \infty$
5. $E[H_{ij}(\theta)] < \infty$ and $E[H_{ijk}(\theta)]$.
6. Both the propensity and prognostic score models are fit on the pilot set $\mathcal{P}$.

Note that these are simply the requirements for theorem 2 from Antonelli et al. without those specific to the use of the high-dimensional lasso. Assumption 6 is necessary to ensure that the matching discrepancies $D_{ij}$ for a fixed $i$ are independent. In practice, it is likely that the researcher will choose to estimate the prognostic score on $\mathcal{P}$ and the propensity score model on the entire data set ($\mathcal{P} \cup D'$).

B.2 Proof for Theorem 2

APPENDIX B.2 EXPLANATION FOR THEOREM 2

The derivation for the form of theorem 2 stated in this text essentially follows the proof for theorem 2 from Antonelli et al. with a few small changes. First, while theorem 2 from Antonelli et al. requires the prognostic and propensity score models to be estimated on a separate data set, our form of theorem 2 makes this explicit by specifying the sample sizes of the analysis and
pilot data sets separately. Second, we note that the specific use of the lasso for fitting the propensity and prognostic models is only used in the part of the proof which derives the asymptotic properties of

$$\tau_{\Phi}(\hat{\theta}; h_{n,\ddot{\theta}}) - \tau_{\Phi}(\ddot{\theta}; h_{n,\ddot{\theta}}),$$

where $\tau_{\Phi}(\theta; h_{n,\ddot{\theta}})$ is a smoothed matching estimator parametrized by $h_{n,\ddot{\theta}}$ and the model parameters $\theta$ used in the propensity and prognostic models. This estimator is described by Antonelli et al. in the Web appendix and we will not define it here. Antonelli et al. show that

$$\tau_{\Phi}(\hat{\theta}; h_{n,\ddot{\theta}}) - \tau_{\Phi}(\ddot{\theta}; h_{n,\ddot{\theta}}) = o_p(1)(\hat{\theta} - \ddot{\theta}) + O_p(\|\hat{\theta} - \ddot{\theta}\|^2).$$

(Again, this fact does not rely on the use of the lasso to estimate $\hat{\theta}$ or any of the assumptions necessary for the consistency estimation from the lasso).

Rather than assuming that $\hat{\theta}$ is estimated with a lasso, we suppose that $\hat{\theta}$ is estimated by some method so that the estimate converges in probability to $\ddot{\theta}$ at rate $R(n_p)$. This gives

$$\tau_{\Phi}(\hat{\theta}; h_{n,\ddot{\theta}}) - \tau_{\Phi}(\ddot{\theta}; h_{n,\ddot{\theta}}) = o_p(R(n_p)).$$

Substituting this in the proof from Antonelli et al. gives the form of Theorem 2 provided here.

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