Abstract

In a block-randomized controlled trial, individuals are subdivided by prognostically important baseline characteristics (e.g., age group, sex, or smoking status), prior to randomization. This step reduces the heterogeneity between the treatment groups with respect to the baseline factors most important to determining the outcome, thus enabling more precise estimation of treatment effect. The stratamatch package extends this approach to the observational setting by implementing functions to separate an observational data set into strata and interrogate the quality of different stratification schemes. Once an acceptable stratification is found, treated and control individuals can be matched by propensity score within strata, thereby recapitulating the block-randomized trial design for the observational study. The stratification scheme implemented by stratamatch applies a “pilot design” approach (Aikens, Greaves, and Baiocchi 2019) to estimate a quantity called the prognostic score (Hansen 2008), which is used to divide individuals into strata. The potential benefits of such an approach are twofold. First, stratifying the data enables more computationally efficient matching of large data sets. Second, methodological studies suggest that using a prognostic score to inform the matching process increases the precision of the effect estimate and reduces sensitivity to bias from unmeasured confounding factors (Aikens et al. 2019; Leacy and Stuart 2014; Antonelli, Cefalu, Palmer, and Agniel 2018). A common mistake is to believe reserving more data for the analysis phase of a study is always better. Instead, the stratamatch approach suggests how clever use of data in the design phase of large studies can lead to major benefits in the robustness of the study conclusions.

Keywords: causal inference, matching, stratification, pilot designs, prognostic score, R.
1. Introduction

In an observational study, researchers are not allowed to dictate which individuals receive a treatment and which do not. This gives rise to concerns that the results of an observational study may be biased due to confounding factors - characteristics of the individuals in the study that influence both their selection of treatment and their probable outcome. Matching methods seek to account for this self-selection by grouping treated and control individuals with similar baseline characteristics. In particular, propensity score matching pairs individuals who appear to have had similar probabilities of receiving the treatment according to their baseline characteristics (Rosenbaum and Rubin 1983). Balancing the treated and control groups in this way attempts to coerce the data set into a form that resembles a fully-randomized controlled trial (King and Nielsen 2016; Rosenbaum et al. 2010). Importantly, however, propensity score matching can only address bias due to measured baseline covariates. Imbalances in unmeasured baseline characteristics may still bias the effect estimate after propensity score matching. To interrogate the potential of bias due to unmeasured confounding, researchers may carry out sensitivity analyses. (For a full discussion of sensitivity analyses, see Rosenbaum (2005b) or Rosenbaum et al. (2010).)

However, the fully-randomized experiment is not the only experimental study design. In a block-randomized controlled experiment, individuals are stratified prior to randomization. Commonly, such strata are based on prognostically important covariates (e.g., for a clinical trial: sex, age group, smoking status). This step helps reduce the heterogeneity between the individuals in the treatment and control groups, particularly the kind of heterogeneity that gives rise to variation in the outcome. This type of balancing between groups has different benefits in the experimental and observational settings. In the experimental context, reducing heterogeneity between compared groups helps to increase the precision of the treatment effect estimate. In observational settings, reducing this type of heterogeneity has the added benefit of reducing the sensitivity of the study results to bias stemming from unobserved confounding variation (see Rosenbaum (2005a) for a full discussion). Moreover, if the sample size of an observational study is very large, stratifying the sample and matching separately within the strata in this way can be much faster computationally than matching the entire sample at once.

The `stratamatch` package extends the block-randomized trial design to the observational setting. It is built to guide users in the process of (1) stratifying an observational data set, (2) assessing the quality of the strata, and (3) matching within each stratum. A primary contribution of `stratamatch` is that it implements a type of ‘pilot design,’ which is introduced in the following section (section 2). Section 3 briefly summarizes important notes on the package implementation, although more information can be found in the package documentation. In section 4, we illustrate the use of `stratamatch` in simulated and applied example settings, and in section 5 we use this applied example to highlight key design choices and advanced functionality of `stratamatch` (section 5). Finally, section 6 offers suggestions and interpretations in the case that the results of a stratification are unsatisfactory, and section 7 gives some concluding remarks.

By dividing individual observations from a study into appropriate strata, the `stratamatch` approach can substantially decrease the computational burden of optimally matching large data sets. However, the main objective of `stratamatch` is not to implement a computationally complex task but to make sophisticated study design concepts accessible to a wider variety of
researchers. There are many packages already available in R for matching observational data sets based on various criteria (e.g., \texttt{optmatch}(Hansen and Klopfer 2006), and \texttt{matchit}(Ho, Imai, King, Stuart \textit{et al.} 2011)). The \texttt{stratamatch} package is not intended to compete with those implementations - indeed, users are encouraged to apply other matching packages in conjunction with \texttt{stratamatch} if desired (see section 5.3). Rather, the primary contribution of \texttt{stratamatch} is the implementation of a prognostic score stratification pilot design (see section 2), which has not yet been provided in an existing package. In doing so, \texttt{stratamatch} supplies a framework for applying the relatively new concept of the pilot design for the stratification of a data set and suggests a series of diagnostics to interrogate the quality of the resulting stratification schemes.

2. Study design

2.1. A prognostic score stratification pilot design

Once the decision has been made to stratify the data set, the question becomes: What baseline characteristics should be used to divide the strata? One option is to select prognostically important covariates by hand, based on expert knowledge. Another option is to use insight from previous experiments in order to determine the best criteria for stratification. In the experimental setting, this may be done with a pilot study. In this approach, researchers set aside some of their resources before running the main experiment in order to run a smaller, "pilot" experiment. By examining the outcomes of the pilot study, they can gather information which they can use to inform the design of the main experiment. Importantly, after the pilot study is run, the individuals in the pilot experiment are not reused in the main experiment, so that the observations of the outcomes from the pilot study are not allowed to bias the results of the main study.

Aikens \textit{et al.} (2019) extend the idea of the pilot study to the observational setting. To help familiarize readers with the vocabulary used to describe this design, descriptions of several terms are collated in table 1. Central to the pilot design concept is the goal of maintaining a separation between the design and analysis phases of a study (see table 1, or for more information Goodman, Schneeweiss, and Baiocchi (2017) and Rubin \textit{et al.} (2008)). Using an observational pilot design, the researchers may partition their data set into an ‘analysis set’ and a held-aside ‘pilot set.’ Outcome information in the pilot set can be observed, and the information gained can be used to inform the study design. Subsequently, in order to preserve the separation of the study design from the study analysis, the individuals from the pilot set are omitted from the main analysis (i.e., they are not reused in the analysis set). The primary insight of the pilot design is that reserving all of the observations in a study for the analysis phase (i.e., in the analysis set) is not always better. Rather, clever use of data in the design phase (i.e., in the pilot set) can lead to major benefits.

The \texttt{stratamatch} package uses a pilot design to estimate a quantity called the prognostic score (proposed by Hansen (2008)), defined here as an individual’s expected outcome under the control assignment, with respect to their baseline covariates. Because of this nature of the prognostic score, the prognostic model must be fit on control individuals only, and then extrapolated to the treatment group. In the \texttt{stratamatch} approach, a random subsample of controls is extracted as a pilot set to fit a prognostic model, and that model is then used
**stratamatch**: Stratified Pilot Matching in \( R \)

| Term             | Description                                                                                                                                 |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Design phase     | Phase of a study in which the analyst considers what kinds of data will provide the strongest information to address the question at hand (e.g., randomization, sampling, matching, inverse probability weighting). Often, the goal of the design phase is to obtain data which will provide strong inference. |
| Analysis phase   | Phase of a study in which the data that comes from the design phase are summarized into statistics. Inference is performed, and (often in the case of observational studies) sensitivity analyses are performed. |
| Pilot Design     | Approach to an observational study in which some data is spent in the design phase to improve the study design/preprocessing.                    |
| Pilot Set        | A subset of observational data extracted to be used in the design phase.                                                                     |
| Analysis set     | The set of observational data reserved to be used for inference in the analysis phase.                                                       |
| Propensity score | Probability of assignment to the treatment group based on measured baseline characteristics.                                                 |
| Prognostic score | Expectation of the outcome in the absence of treatment based on measured baseline characteristics.                                             |
| Prognostic model | A model (e.g., a logistic regression fit) used to estimate prognostic scores.                                                                   |
| Stratum          | A subset of observations in the analysis set to be matched together. In the \textit{stratamatch} approach, the strata are determined based on prognostic score, and matching within strata is based on propensity score. |

Table 1: Summary of relevant methodological terms as they apply to \textit{stratamatch}.

to estimate prognostic scores on the mix of control and treated individuals in the analysis set. The observations in the analysis set can then be stratified based on the quantiles of the estimated prognostic score, and matched by propensity score within strata (see section 3).

2.2. When to use this approach, and why

\textit{Aikens et al.} (2019) go into detail on the scenarios in which a prognostic score matching pilot design is most useful. Briefly, the \textit{stratamatch} approach is best for large data sets (i.e., thousands to millions of observations), especially when the number of control observations is plentiful. Such data sets are already becoming more commonplace, for example, in studies of electronic medical record data. When - as is often the case - the number of controls far exceeds the number of treated observations, each additional control observation reserved for the analysis phase (i.e., in the ‘analysis set’) has a vanishingly small benefit towards increasing the precision of estimation. In these scenarios, extracting some control observations in the design phase (i.e., in the ‘pilot set’) can be more advantageous because balancing treated and control groups on prognostic score not only increases precision but efficiency and robustness:

1. **Benefits to inference**: Balancing observational data sets based on prognostic score
can then reduce heterogeneity between matched individuals, allowing for more precise
inference and diminishing the sensitivity of the study results to unobserved confounding
(Aikens et al. 2019; Leacy and Stuart 2014; Antonelli et al. 2018). As an additional
benefit, mathematical results and simulation studies suggest that using the prognostic
score and the propensity score in combination helps the study results to be robust in
the case that either the propensity score or the prognostic score model is incorrect (i.e.,
estimation is doubly-robust, see Aikens et al. (2019); Leacy and Stuart (2014); Antonelli
et al. (2018)).

2. **Benefits to computation:** In data sets of more than a few thousand individuals, the
task of optimally matching the individuals is greatly accelerated by stratifying prior to
matching. Since the prognostic score is often continuous, prognostic score quantile ‘bins’
can be easily used to select evenly sized strata. This circumvents common problems
with stratification based on expert knowledge, since that process often generates strata
which are too large, too small, or too poorly balanced between treatment and control
observations (see, for example, the stratification diagnostics in section 4.2).

3. **Software**

The `stratamatch` function, `auto_stratify`, implements the prognostic score stratification in
the pilot design described above. Although there are many additional options available when
running this function, the most basic procedure does the following:

1. Partition the data set into a pilot data set and an analysis data set
2. Fit a model for the prognostic score from the observations in the pilot set
3. Estimate prognostic scores for the analysis set using the prognostic model
4. Stratify the analysis set based on prognostic score quantiles.

The `auto_stratify` function is thus the primary workhorse of the `stratamatch` package. The
basic usage is:

```r
auto_stratify(data, treat, prognosis, outcome = NULL, size = 2500,
pilot_fraction = 0.1, pilot_sample = NULL)
```

A call to `auto_stratify` produces an `auto_strata` object, which contains the analysis set,
the pilot set, and other information about the strata and prognostic scores. The `stratamatch`
package implements several diagnostics that can be run on an `auto_strata` object
to interrogate the quality of the stratification produced. The arguments to `auto_stratify`,
the contents of an `auto_strata` object, and the diagnostics for stratified data sets are
described further in the `stratamatch` documentation, and two illustrative examples are provided
in section 4.

Once the data set has been stratified, `stratamatch` suggests several diagnostic plots and tables
that can be used to assess the size and balance of the strata produced. If the strata are
satisfactory, the treatment and control individuals within each stratum can then be matched.
stratamatch: Stratified Pilot Matching in R

To do this, the reader may perform a 1 : k propensity score matching within each stratum using the \texttt{strata_match} function, or - if something more complex is desired - they may select and implement their own matching scheme (see section 5.3 for a brief discussion on matching strategies).

4. Illustrations

4.1. Simulated example

This section demonstrates the basic functionality of \texttt{stratamatch} in simulated example. This package contains a function, \texttt{make_sample_data}, which generates a simple simulated data set of any specified number of observations, so that users can explore the design options implemented by \texttt{stratamatch}. Below, we generate a sample of 10,000 observations and print the first few rows as an illustration.

R> library("stratamatch")
R> library("dplyr")
R> dat <- make_sample_data(n = 10000)
R> head(dat)

|   | X1     | X2     | B1 | B2 | C1 | treat | outcome |
|---|--------|--------|----|----|----|-------|---------|
| 1 | 0.93332697 | 1.0728339 | 1  | 0  | a  | 1     | 0       |
| 2 | -0.52503178 | 0.3449057 | 1  | 1  | b  | 0     | 1       |
| 3 | 1.81443979  | 1.0361942 | 1  | 1  | a  | 1     | 0       |
| 4 | 0.08304562  | 0.3017060 | 1  | 1  | a  | 0     | 1       |
| 5 | 0.39571880  | 0.5397257 | 0  | 0  | c  | 0     | 0       |
| 6 | -2.19366962 | 1.4523274 | 1  | 1  | b  | 0     | 1       |

The user should suppose that the rows of \texttt{dat} are individuals in an observational study, and the objective of the study is to estimate the effect of a binary treatment assignment (\texttt{treat}) on a binary outcome (\texttt{outcome}). However, in an observational data set, individuals are allowed to self-select into treatment and control groups, perhaps influenced by their background characteristics. Thus, we cannot naively compare the treated and control groups in this data set, because there may be differences between these individuals in terms of their baseline characteristics. We are in the common observational setting in which there are many more control observations versus treated units - \texttt{dat} is a fairly large data set (10,000 observations), but only about 1/5 of the individuals in the data set received the treatment.

In addition to treatment assignments and outcomes, we have measured five baseline covariates for each individual: \texttt{X1} and \texttt{X2} are continuous, \texttt{B1} and \texttt{B2} are binary, and \texttt{C1} is a categorical variable which takes on possible values “a”, “b”, and “c”. For this example, we assume strongly ignorable treatment assignment - that is, roughly, there are no unmeasured confounding factors (Rosenbaum and Rubin 1983). (To appropriately address this assumption, one might run a sensitivity analysis - see, for example Rosenbaum (2005b)).

Automatic stratification

We begin our pilot design by running the \texttt{auto_stratify} function. The command below uses \texttt{auto_stratify} to (1) partition 10% of the controls in \texttt{dat} into the pilot set (2) fit a prognostic
score model for outcome based on X1 and X2, (3) estimate prognostic scores on the analysis set, and (4) return to us the analysis set, divided into strata of approximately 500 individuals, based on prognostic score quantiles. All of these steps are completed automatically with this function call, and the results are returned to us as `a.strat`.

```r
R> a.strat <- auto_stratify(dat, treat = "treat",
+                          prognosis = outcome ~ X1 + X2,
+                          pilot_fraction = 0.1, size = 500)

Constructing a pilot set by subsampling 10% of controls.
Fitting prognostic model via logistic regression: outcome ~ X1 + X2
```

The result returned by `auto_stratify` is an `auto_strata` object. Running `print` on this object gives us some basic information about how the stratification process has been completed.

```r
R> print(a.strat)
auto_strata object from package stratamatch.

Function call:
auto_stratify(data = dat, treat = "treat", prognosis = outcome ~
X1 + X2, size = 500, pilot_fraction = 0.1)

Analysis set dimensions: 9234 X 8

Pilot set dimensions: 766 X 7

Prognostic Score Formula:
outcome ~ X1 + X2

Number of strata: 19

  Min size: 486     Max size: 486
```

Here, `auto_stratify` has partitioned away a pilot set of 766 control individuals to fit our desired prognostic model, leaving 9,234 individuals in the analysis set. Once the prognostic scores were estimated on the analysis set, these 9,234 remaining individuals were partitioned into 19 strata based on prognostic score quantiles, each with 486 individuals. In order to record these stratification assignments, an eighth column, `stratum`, has been appended to the analysis set.

We can access the analysis set and pilot set from `a.strat` via `a.strat$analysis_set` and `a.strat$pilot_set`, respectively. Another important piece of information on the stratification process is stored in the `strata_table`, which reports the strata sizes and the prognostic score quantile bins which define each stratum. For example, we see below that stratum 1 contains the 486 individuals with the lowest prognostic scores (values from 0.00978 to 0.137).

```r
R> a.strat$strata_table
# A tibble: 19 x 3
```
**stratamatch**: Stratified Pilot Matching in R

```
stratum quantile_bin size
  <int> <chr> <int>
1   1  [0.00978,0.137) 486
2   2  [0.13735,0.199) 486
3   3  [0.19880,0.247) 486
4   4  [0.24690,0.288) 486
5   5  [0.28821,0.334) 486
6   6  [0.33354,0.374) 486
7   7  [0.37425,0.416) 486
8   8  [0.41601,0.457) 486
9   9  [0.45740,0.496) 486
10 10  [0.49630,0.535) 486
11 11  [0.53496,0.571) 486
12 12  [0.57082,0.611) 486
13 13  [0.61136,0.653) 486
14 14  [0.65333,0.691) 486
15 15  [0.69121,0.730) 486
16 16  [0.73036,0.774) 486
17 17  [0.77402,0.819) 486
18 18  [0.81862,0.873) 486
19 19  [0.87341,0.990] 486
```

**Diagnostics**

The **stratamatch** package implements various suggested diagnostics to interrogate the quality of a stratification. The most straightforward diagnostic is the **issue_table**, which can be accessed as follows:

```R
R> a.strat$issue_table
# A tibble: 19 x 6
   Stratum Treat Control Total Control_Proportion Potential_Issues
   <int> <int> <int> <int>       <dbl>            <chr>
1       1     1   167   319   486 0.656 none
2       2     2   149   337   486 0.693 none
3       3     3   160   326   486 0.671 none
4       4     4   132   354   486 0.728 none
5       5     5   123   363   486 0.747 none
6       6     6   122   364   486 0.749 none
7       7     7   146   340   486 0.700 none
8       8     8   109   377   486 0.776 none
9       9     9   131   355   486 0.730 none
10     10    10   132   354   486 0.728 none
11      11    11   111   375   486 0.772 none
12      12    12   108   378   486 0.778 none
13      13    13   112   374   486 0.770 none
14      14    14   122   364   486 0.749 none
```
Here, we see the total size and composition of each stratum. The 'Potential_Issues' column is meant to quickly flag strata which may be too large, too small, or too dominated by treated or control samples. The "Not enough treated samples" appears when a stratum includes 4 or more controls for every 1 treated individual. This is a relatively common issue, which is often easily addressed. This topic is discussed further in sections 5.3 and 6. (Note that the specific 1:4 ratio cutoff is entirely arbitrary; this warning flag is simply meant to draw researchers' attention to strata which are relatively imbalanced.)

The \texttt{stratamatch} package implements four plotting options to interrogate different properties of the stratification process and the data set. They are:

1. \textbf{Size-Ratio Plots:} (Figure 1) This default plot shows each stratum in the analysis set based on its size and the percentage of control observations. This plot recapitulates the issue table in a visual format, allowing users to easily identify strata which may be challenging to match effectively.

2. \textbf{Propensity score histograms:} (Figure 2) This plot shows the distribution of estimated propensity scores (from logistic regression) across the treatment and control groups within a stratum, for assessing propensity score overlap.

3. \textbf{Fisher-Mill Plots:} (Figure 3) Based on the visualizations from Aikens \textit{et al.} (2019), this plot shows each individual in the treated and control groups within a stratum in terms of their estimated propensity score and their estimated prognostic score. Fisher-Mill plots are meant to check the overlap of the individuals in the data set in terms of both their prognostic scores and their propensity scores.

4. \textbf{Residual Plots:} (Not shown) This option shows the diagnostic plots for the prognostic model used to perform the stratification. It is essentially a wrapper for \texttt{plot.lm}. For more information and examples of this plot type, see the documentation for \texttt{plot.lm} in the base R package, \texttt{stats}.

The code below makes each of the plot types listed above (in order). For propensity score histograms and Fisher-Mill plots, information on the propensity scores is required. This may take the form of a formula for a logistic propensity score model (to be fit automatically on the analysis set), a model for propensity, or a vector of estimated propensity scores. In the code below, the propensity score is fit based on a regression of treatment assignment on X1, X2, B1, and B2. Section 6 offers suggested interpretations or solutions for cases when the diagnostic plots indicate potential issues with the data set or stratification.

\begin{verbatim}
R> plot(a.strat, type = "SR")
R> plot(a.strat, type = "hist",
+       propensity = treat ~ X2 + X1 + B1 + B2,
\end{verbatim}
stratamatch: Stratified Pilot Matching in R

+ stratum = 1)
R> plot(a.strat, type = "FM",
+ propensity = treat ~ X2 + X1 + B1 + B2,
+ stratum = 1)
R> plot(a.strat, type = "residual")

Figure 1: A size-ratio plot. Each point represents a stratum. Yellow regions highlight strata in which there are 4 or more controls for every one treated individual, or vice versa. Red zones highlight strata which are small enough that finding high quality matches may be difficult, and strata which are so large that optimal matching is likely to be very computationally intensive. These colors are meant to be evocative: yellow being a warning and red indicating strata that might be quite problematic. In a perfectly ideal stratification, all strata would fall within the white rectangle. In practice, some strata often fall within one of the yellow regions because observational data sets often have many more control than treated observations.

Finally, when a prognostic model is fit by auto_stratify, the model can be easily accessed from the output. This allows the user to perform more specific diagnostics on the prognostic model as desired. As a simple example, the code below extracts the prognostic model and prints a summary of the fit.

R> prog_model <- a.strat$prognostic_model
R> summary(prog_model)
Call:
glm(formula = prognostic_formula, family = "binomial", data = dat)

Deviance Residuals:
       Min        1Q    Median        3Q       Max
-2.3785    -0.9761     0.4481     0.9893     2.6504
Figure 2: A histogram of estimated propensity scores for a selected stratum. This shows the
distribution of propensity scores between treated and control groups. In an ideal scenario,
there is ample overlap between treated and control individuals within each stratum.

Figure 3: A Fisher-Mill plot (Aikens et al. 2019) showing estimated propensity score versus
estimated prognostic score for each subject in a selected stratum. In an ideal scenario, there
is ample overlap between treated and control individuals in terms of both prognosis and
propensity (for other cases, see section 6). Note that it is normal for the prognostic scores to
appear cut off at the upper and lower the edges of the Fisher-Mill plot for a single stratum
because each stratum is defined using prognostic score quantiles.
stratamatch: Stratified Pilot Matching in R

Coefficients:

|                | Estimate | Std. Error | z value | Pr(>|z|) |
|----------------|----------|------------|---------|----------|
| (Intercept)    | 0.006991 | 0.116263   | 0.06    | 0.952    |
| X1             | -1.156612| 0.104456   | -11.07  | <2e-16   *** |
| X2             | 0.054949 | 0.073237   | 0.75    | 0.453    |

---

Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

Null deviance: 1060.02 on 765 degrees of freedom
Residual deviance: 891.61 on 763 degrees of freedom
AIC: 897.61

Number of Fisher Scoring iterations: 4

Matching

Once the data have been stratified, the user can optimally match individuals within each stratum using the strata designations in the analysis set. A 1-to-1 or 1-to-k optimal propensity score matching within strata can be done automatically with the strata_match function, as in the example below. As before, we assume the propensity score model treat ~ X1 + X2 + B1 + B2. This function makes essential use of the optmatch package (Hansen and Klopfer 2006) to perform the matching within strata. For further discussion on more complicated matching schemes, see section 5.

R> mymatch <- strata_match(a.strat, k = 1,
+                          propensity = treat ~ X1 + X2 + B1 + B2)

This function makes essential use of the optmatch package, which has an academic license.
For more information, run optmatch::relaxinfo()
Fitting propensity model: treat ~ X1 + X2 + B1 + B2 + strata(stratum)

The result is an optimal 1 to 1 matching within prognostic score strata. The results of this matching are summarized below:

R> summary(mymatch)
Structure of matched sets:
  1:1 0:1
2339 4556
Effective Sample Size: 2339
(equivalent number of matched pairs).

Above, mymatch is an optmatch class object, as described by the optmatch package (Hansen and Klopfer 2006). For the most part, mymatch can be treated as a factor giving match assignments for each row of the data set. The summary above (also described by optmatch)
states that each of the 2339 treated individuals in the data set were matched to a single
control individual in the same stratum, giving 2339 matched pairs and 4556 unmatched left-
over controls. For more suggestions on matching schemes for stratified data, see 5.3.

4.2. Real-data example: Life sustaining treatments for critical care patients

The following example is a reanalysis of deidentified data collected by Chavez, Richman,
Kaimal, Bentley, Yasukawa, Altman, Periyakoil, and Chen (2018) on life sustaining treat-
ments for intensive care unit (ICU) patients. Briefly, the authors sought to understand the
correlates of different treatment decisions for critically ill patients. To do this, they ex-
tracted demographic information, common laboratory test results, comorbidity information,
and treatment team assignments for 10,157 ICU patients from the Stanford University Hos-
pital who met their inclusion criteria. A re-processed version of this data set which is used in
the following examples is available with the stratamatch package (version 0.1.3 or greater).

During their stay, each patient’s critical care preferences are summarized with a code status.
The default - Full Code status - indicates no limitations on resuscitative measures, while
other codes indicate different limitations on what intensity and type of resuscitation the
patient should receive in the event that they become pulseless or apneic (i.e., their heart
stops or they stop breathing). This code status is a product of complex dynamics between
patient and provider. When a patient’s code status does not effectively reflect their goals
of care, patients may have life sustaining care inappropriately withheld, or they may receive
aggressive, harmful treatment which does not effectively increase their quality or quantity of
remaining life.

In this example, suppose a researcher wants to study whether comparable patients under the
care of surgical teams vs. non-surgical teams are more likely to have their code status set to
limit resuscitation (i.e., any form of any form of ‘Do not resuscitate’, or ‘DNR’). Such varia-
tion in code status selection could reflect the tendencies that different treatment teams have
in counseling and making decisions about life-sustaining treatments for critically ill patients.
However, the patient groups seen by surgical vs. non-surgical teams are necessarily different,
because patients are assigned to treatment teams based on their reason for being in the hos-
pital and their treatment history. Thus, a naive comparison of DNR order frequency between
care team types would be misleading. To better account for these potential differences, we
employ a stratified pilot matching design. Patients are first stratified by a prognostic score
(i.e., their estimated probability of receiving a DNR order if they are not assigned to a surgical
care team), and then matched based on propensity score (i.e., a model of their probability of
assignment to a surgical care team).

Automatic stratification

Before matching, we stratify patients with similar likelihood of the outcome of interest (i.e.,
a subsequent DNR order, in the absence of assignment to a surgical care team). In the
example below, we use auto_stratify on the ICU_data to (1) partition 10% of controls into
a pilot set, (2) build a prognostic score model on that pilot set based on age, sex, and race
(3) estimate prognostic scores on the analysis set and (4) return a stratified data set with
approximately 500 individuals per stratum.
`stratamatch`: Stratified Pilot Matching in R

```r
R> ICU_astrat <- auto_stratify(data = ICU_data,
+    treat = "surgicalTeam",
+    prognosis = DNR ~ Birth.preTimeDays +
+        Female.pre + RaceAsian.pre +
+        RaceUnknown.pre + RaceOther.pre +
+        RacePacificIslander.pre + RaceBlack.pre +
+        RaceNativeAmerican.pre + all_latinos,
+    pilot_fraction = 0.1,
+    size = 500)

Constructing a pilot set by subsampling 10% of controls.
Fitting prognostic model via logistic regression: DNR ~ Birth.preTimeDays +
    Female.pre + RaceAsian.pre + RaceUnknown.pre + RaceOther.pre +
    RacePacificIslander.pre + RaceBlack.pre +
    RaceNativeAmerican.pre + all_latinos

Next, we print the results.

R> print(ICU_astrat)
auto_strata object from package stratamatch.

Function call:
auto_stratify(data = ICU_data, treat = "surgicalTeam",
    prognosis = DNR ~ Birth.preTimeDays +
        Female.pre + RaceAsian.pre + RaceUnknown.pre + RaceOther.pre +
        RacePacificIslander.pre + RaceBlack.pre +
        RaceNativeAmerican.pre + all_latinos,
    size = 500, pilot_fraction = 0.1)

Analysis set dimensions: 9364 X 14

Pilot set dimensions: 793 X 13

Prognostic Score Formula:
DNR ~ Birth.preTimeDays + Female.pre + RaceAsian.pre + RaceUnknown.pre +
    RaceOther.pre + RaceBlack.pre + RacePacificIslander.pre +
    RaceNativeAmerican.pre + all_latinos

Number of strata: 19

    Min size: 492     Max size: 494

We see here that auto_stratify partitioned the data into a pilot set of 793 “controls”
(i.e., patients not assigned to a surgical treatment team) and an analysis set of the 9,364
remaining individuals. The prognostic model was fit on the pilot set according to the formula
we provided, regressing DNR code assignment on age, sex, and race. This model was used to
estimate the prognostic score (probability of DNR code assignment based on demographics)
for each of the 9,364 individuals in the analysis set. Finally, each individual in the analysis
set was assigned to a stratum based on this score. 19 strata, each containing between 492
and 494 patients, were created. This stratum assignment information was appended to the analysis set by adding a new 14th column, \texttt{stratum}.

\textit{Manual stratification}

For researchers who wish to stratify the data set based on discrete covariates (e.g., chosen by a domain expert) rather than a prognostic score, \texttt{stratamatch} supports this through the \texttt{manual\_stratify} function. For example, one could bin the 10,157 patients in the data set purely based on race and sex, placing all Caucasian males in stratum 1, all Native American males in stratum 2, and so on. Note that while it was simple to incorporate age into the prognostic model for automatic stratification, we cannot use age directly to create these bins, because it is a continuous variable. Rather, in order to incorporate age information in the stratification, one would have to divide the sample into discrete age bins. However, settling upon a binning scheme which results in appropriately sized strata may be a time-consuming iterative process. For simplicity, the code below stratifies manually using only race and sex.

\begin{verbatim}
R> ICU_mstrat <- manual_stratify(data = ICU_data, 
+   strata_formula = surgicalTeam ~ Female.pre + 
+   RaceAsian.pre + RaceUnknown.pre + 
+   RaceOther.pre + RaceBlack.pre + 
+   RacePacificIslander.pre + 
+   RaceNativeAmerican.pre + all_latinos)

R> print(ICU_mstrat)
manual_strata object from package stratamatch.

Function call:
manual_stratify(data = ICU_data, strata_formula = surgicalTeam ~ 
Female.pre + RaceAsian.pre + RaceUnknown.pre + RaceOther.pre + 
RaceBlack.pre + RacePacificIslander.pre + RaceNativeAmerican.pre + 
all_latinos)

Analysis set dimensions: 10157 X 14

Number of strata: 16

Min size: 17        Max size: 3314
\end{verbatim}

The results of a manual stratification have no pilot set, since no pilot set is used and no prognostic score is fit. However, just as with the results of \texttt{auto\_stratify}, the command \texttt{ICU\_mstrat\$analysis\_set} gives the analysis set with an extra column added for stratum assignment, and the command \texttt{ICU\_mstrat\$strata\_table} gives the sizes and definitions of each of the strata in terms of the covariates they respond to. Size-ratio plots and propensity score histograms are supported for manually stratified data sets. However, Fisher-Mill and residual plots depend on a prognostic score model, so they cannot be made from the results of a manual stratification. Any result from \texttt{manual\_stratify} can also be passed as an argument to \texttt{strata\_match} to perform within-strata optimal matching. The diagnostics in the following section highlight some common challenges that emerge when manually stratifying a data set.
Diagnostics

The size-ratio plots for the manual and automatic stratification illustrate a common issue with manual stratification: it is often a very difficult task to select discrete covariates which result in appropriately sized and balanced strata (Figure 4). This also is reflected in the issue table for the manual stratification below. For example, the stratum containing white males (stratum 1) contains 3,314 patients, while the stratum of Native American males (stratum 3) contains only 18 patients, only one of whom was assigned to a surgical team. In exceedingly large strata, matching becomes increasingly computationally intensive, while in exceedingly small and/or highly imbalanced strata, finding high quality matches can be infeasible.

R> ICU_mstrat$issue_table
# A tibble: 16 x 6

Stratum Treat Control Total Control_Proportion Potential_Issues
<int> <int> <int> <int> <dbl> <chr>
1 1 761 2553 3314 0.770 none
2 2 212 672 884 0.760 none
3 3 1 17 18 0.944 Too few samples; Not enough treated samples
4 4 13 67 80 0.838 Not enough treated samples
5 5 56 205 261 0.785 none
6 6 65 286 351 0.815 Not enough treated samples
7 7 29 226 255 0.886 Not enough treated samples
8 8 174 563 737 0.764 none
9 9 508 1842 2350 0.784 none
10 10 158 470 628 0.748 none
11 11 4 13 17 0.765 Too few samples
12 12 15 54 69 0.783 Too few samples
13 13 37 194 231 0.840 Not enough treated samples
14 14 46 195 241 0.809 Not enough treated samples
15 15 16 173 189 0.915 Not enough treated samples
16 16 131 401 532 0.754 none

In contrast, the size-ratio plots for the automatic stratification show a much smaller range of sizes and control proportions. In the issue table for the automatically stratified data set (not shown), the highest-numbered strata (i.e., those containing the individuals with the highest prognostic scores) contain the smallest proportion of treated individuals. This underscores why a naive comparison of ICU patients assigned to surgical and non-surgical treatment teams would be misleading: the patients with the highest prognostic score (i.e., those most likely to have a DNR code based on their age, race, and sex) are the least likely to be under the care of a surgical team.

The code below displays the Fisher-Mill plot for one of the strata in the automatically stratified data set (Figure 5).

R> plot(ICU_astrat, type = "FM", propensity = surgicalTeam ~ Female.pre + Birth.preTimeDays + RaceAsian.pre + RaceUnknown.pre + RaceOther.pre + RaceBlack.pre + RacePacificIslander.pre + RaceNativeAmerican.pre + all_latinos, stratum = 2)
For simplicity, we assume a propensity score formula which is also based on age, sex, and race. Fisher-Mill plots like this one with many striae of observations are not uncommon. When many of the variables used in the prognostic or propensity model are discrete (e.g., sex and race), the scores for observations may be grouped based on the important discrete covariates. For these reasons, jitter arguments can be supplied when making the Fisher-Mill plots in order to avoid “stacking” of multiple data points ("jittering" adds small amounts of random noise to the coordinates of each point so that data points aren’t stacked upon each other).

Matching

In the previous section, we used auto_stratify to separate the data set into 19 groups of approximately 500 individuals which - based on their age, sex, and race - appeared to have similar likelihood of having a DNR status code in the ICU. Since every stratum contains at least a 1:2 ratio of patients who were assigned to surgical teams and those who were not, we can match 2 “control” (i.e., non-surgical team) patients to each “treated” (i.e., surgical team) subject in each stratum. In this step, we match individuals who, based on their baseline covariates, appear equally likely to have been assigned to a surgical team vs. not.

The following performs the matching:

```R
R> ICU_match <- strata_match(ICU_astrat,
+     propensity = surgicalTeam ~ Birth.preTimeDays +
+     Female.pre + RaceAsian.pre + RaceUnknown.pre +
+     RaceOther.pre + RaceBlack.pre
+     RacePacificIslander.pre + RaceNativeAmerican.pre +
+     .
+     all_latinos,
+     k = 2)
```
Figure 5: Fisher–Mill plot for automatic stratification of ICU data. The striations are caused by heavily weighted discrete features in the prognostic model, which cause points to align together.

This function makes essential use of the optmatch package, which has an academic license.
For more information, run optmatch::relaxinfo()
Fitting propensity model: surgicalTeam ~ Birth.preTimeDays + Female.pre + RaceAsian.pre + RaceUnknown.pre + RaceOther.pre + RaceBlack.pre + RacePacificIslander.pre + RaceNativeAmerican.pre + all_latinos + strata(stratum)

And here, we print a summary:

R> summary(ICU_match)
Structure of matched sets:
  1:2 0:1
  2226 2686
Effective Sample Size: 2968
(equivalent number of matched pairs).

At this point we can compare our matched treated and control individuals to infer whether patients assigned to surgical treatment teams are more or less likely to be assigned a DNR code status.
5. Key design choices and advanced functionality

5.1. Designing the selection of the pilot set

In the illustrations from section 4 we demonstrated the simplest method of extracting the pilot set: a random subsampling of all controls. Aikens et al. (2019) contains a more thorough discussion of the considerations that might inform the selection of a pilot set. Importantly, if the individuals in the pilot set are very different from the individuals in the treatment group, the prognostic model built on this pilot set will be extrapolating heavily when prognostic scores are estimated on the analysis set. Thus, it can be valuable to construct a pilot set which is representative of the sample on which prognostic scores are to be estimated.

Suppose that a different researcher approaching the question in section 4.2 wants to ensure that the pilot set and the analysis set have the same proportions of men and women, and the same fraction of individuals who are uninsured (“self pay”). This can be done by providing the group_by_covariates argument directly to auto_stratify. However, as an illustration, the code below does this process more explicitly by partitioning the data with the stratamatch function, split_pilot_set:

R> ICU_split <- split_pilot_set(ICU_data, treat = "surgicalTeam",
+         pilot_fraction = 0.1,
+         group_by_covariates = c("Female.pre", "self_pay"))

Constructing a pilot set by subsampling 10% of controls.
Subsampling while balancing on: Female.pre self_pay

Split pilot set returns a list containing the pilot_set and the analysis_set. Once this is done, the results can be passed to auto_stratify as shown below. The command here uses auto_stratify to fit the same prognostic model as in section 4.2, but to use the pilot and analysis sets from the split_pilot_set results above rather than randomly subsampling from the controls (the default).

R> ICU_astrat2 <- auto_stratify(data = ICU_split$analysis_set,
+   treat = "surgicalTeam",
+   prognosis = DNR ~ Birth.preTimeDays +
+       Female.pre + RaceAsian.pre +
+       RaceUnknown.pre + RaceOther.pre +
+       RacePacificIslander.pre + RaceBlack.pre +
+       RaceNativeAmerican.pre + all_latinos,
+   pilot_sample = ICU_split$pilot_set,
+   size = 500)

Using user-specified set for prognostic score modeling.
Fitting prognostic model via logistic regression: DNR ~ Birth.preTimeDays +
    Female.pre + RaceAsian.pre + RaceUnknown.pre + RaceOther.pre +
    RaceBlack.pre + RacePacificIslander.pre + RaceNativeAmerican.pre +
    all_latinos
Another scenario in which this approach can be useful occurs when there is some category of observations in the data which are extremely rare. For example, in the ICU data set there are only a few dozen patients who have Native American ancestry. This means that, in very rare cases, a pilot set sampled perfectly at random might contain none of these Native American patients. In such a scenario, a prognostic model or demographic information fit to that pilot set would fail to estimate the prognostic scores for the Native American patients in the analysis set (in fact, auto_stratify would exit with an error). One straightforward solution is to sample the pilot set so that there are equal proportions of patients with Native American ancestry in the pilot and analysis sets (i.e., using an approach like the one above, but listing RaceNativeAmerican.pre in the group_by_covariates argument).

5.2. Fitting the prognostic model

When fitting a prognostic model with auto_stratify uses a linear regression when the outcome is continuous and a logistic regression when the outcome is binary. However, a researcher may be interested in fitting a more complicated prognostic model, for example the lasso (as suggested by Antonelli et al. (2018); see also Friedman, Hastie, and Tibshirani (2001)). To accommodate a wider variety of modeling schemes, auto_stratify can be run using a vector of prognostic scores for the analysis set that the researcher has obtained by fitting whatever model they desire to a pilot set of their own design.

The example below uses the glmnet package (Friedman, Hastie, and Tibshirani 2010) to fit a cross-validated lasso on the pilot set which was extracted in the previous section.

R> library(glmnet)
R> x_pilot <- ICU_split$pilot_set %>%
  + dplyr::select(Birth.preTimeDays, Female.pre, RaceAsian.pre,
  +   RaceUnknown.pre, RaceOther.pre, RaceBlack.pre,
  +   RacePacificIslander.pre, RaceNativeAmerican.pre,
  +   all_latinos) %>%
  + as.matrix()
R> y_pilot <- ICU_split$pilot_set %>%
  + dplyr::select(DNR) %>%
  + as.matrix()
R> cvfit <- cv.glmnet(x_pilot, y_pilot, family = "binomial")

The prognostic scores can then be estimated on the analysis set.

R> x_analysis <- ICU_split$analysis_set %>%
  + dplyr::select(Birth.preTimeDays, Female.pre, RaceAsian.pre,
  +   RaceUnknown.pre, RaceOther.pre, RaceBlack.pre,
  +   RacePacificIslander.pre, RaceNativeAmerican.pre,
  +   all_latinos) %>%
  + as.matrix()
Finally, these scores can be passed to `auto_stratify` with the `prognosis` argument. This tells `auto_stratify` to divide the analysis set into strata of the desired size based on the quantiles of the scores estimated by hand above.

```r
R> ICU_astrat3 <- auto_stratify(data = ICU_split$analysis_set,  +   treat = "surgicalTeam",  +   outcome = "DNR",  +   prognosis = lasso_scores,  +   pilot_sample = ICU_split$pilot_set,  +   size = 500)
```

### 5.3. Matching

Section 4 demonstrates how the `stratamatch` package can be used for optimal $1:k$ matching on propensity score. However, if the researcher aims to do something very specific or nuanced in the matching process, their best approach may be to carry out this step by hand using other matching software (e.g., `optmatch` (Hansen and Klopfer 2006), `matchit` (Ho et al. 2011)). For example, users proficient with the R package `optmatch` (Hansen and Klopfer 2006) will note that adding `+ strata(stratum)` to the matching formula supplied to `optmatch::pairmatch` and other matching functions will request that the individuals in the data set are matched within their assigned strata. Another approach is to divide the `analysis_set` into separate data frames and match on those individually, perhaps distributing over several computing nodes.

More nuanced matching schemes may also help address imbalances in the number of treated and control units within strata. For example, the researcher could perform fixed $1:k$ matching within each stratum, but allow $k$ to vary between strata - matching more controls to each treated individual in strata where controls are plentiful and performing $1:1$ or $1:2$ matching where treated to control ratios are more balanced. Another solution is to use a matching scheme within strata which naturally allows for variation in the ratio of treated and control individuals in matched sets, such as fullmatching (Rosenbaum 1991) or variable $k$ matching (Pimentel, Yoon, and Keele 2015).

### 6. Trouble-shooting

This section presents a brief overview of the actions one might take when a first attempt to automatically stratify a data set does not lead to satisfactory results. Some of these issues require only a small modification in the study design, while others may point to a more profound imbalance in the data set itself. The solutions we present here are only general recommendations for common scenarios. Researchers are encouraged to use their own discretion and understanding of the question and data set at hand. However, in order to preserve the separation of the design and analysis set, it is important that individuals partitioned in the pilot set can never be recombined with the analysis set. For instance,
simply running `auto_stratify` repeatedly with different seeds to sample new pilot sets from the data and fit new prognostic score models will cause the prognostic model to be overfit to the analysis set, raising concerns of bias in the study results (see, for example, the concerns raised by Hansen (2008)).

A user may encounter the following issues:

1. **Some strata are too small or too large:** Often, this problem can be solved simply by rerunning `auto_stratify` with a different size parameter. When this is done, the researcher should be sure to use the same pilot and analysis set as they received when they first ran `auto_stratify` (i.e., do not partition a new pilot set).

2. **The strata have poor balance of treated and control individuals:** This problem is relatively common, but it is often straightforward to address. For instance, in the illustration in section 4.1, there are two strata in which there is a less than 1:4 ratio of treated to control patients in the automatically stratified data set (Figure 1). We can address this with a matching scheme which pairs more than one control individual with each treated individual. See section 5.3 for some suggestions.

3. **The prognostic model is poor:** In some cases, the user may encounter an error fitting the prognostic model, or they may suspect while running diagnostics on the prognostic model that the model does a poor job of capturing variation in the outcome. There are a few reasons the prognostic model may be problematic.
   
   (a) **The prognostic model was mis-specified.** In this case, the user should fit a revised prognostic model on the same pilot set as was previously used. However, refitting repeatedly can lead to overfitting, so this should be done in moderation.

   (b) **The pilot set was too small to get a good enough fit.** In this case, the user can add more samples from the analysis set to the existing pilot set. Samples that are moved into the pilot set must stay in the pilot set and cannot be re-pooled with the analysis set.

   (c) **Pilot set size is sufficient, but prognostic model perfectly separates treated individuals from control individuals:** If this occurs in either the pilot set or analysis set, it may be a sign that overlap is poor. See below.

4. **The treated and control individuals within strata have poor overlap in propensity and/or prognostic scores:** This problem is best diagnosed with Fisher-Mill plots (see Aikens et al. (2019) for a deeper description). Propensity and prognostic score based subclassification methods both depend on some form of overlap in the baseline characteristics of treated and control individuals in order to make a valid estimate of causal effect. For a brief summary of these requirements for propensity and prognostic score based study designs, see Leacy and Stuart (2014), and for a deeper discussion, see Hansen (2008). In summary, treatment and control groups which are clearly separated in terms of either their propensity scores and/or prognostic scores can be an indication that these two groups should simply not be compared, because the resulting inference on treatment effect would be misleading, regardless of the study design.

7. **Summary and discussion**
Many available R packages focus on implementing computationally complex algorithms for statistical problems. There are already various matching software packages available for these purposes (e.g., optmatch (Hansen and Klopfer 2006), matchit (Ho et al. 2011)). The primary objective of stratamatch is not to directly implement a computationally taxing task, but rather to make more sophisticated study design tools available to a wider variety of researchers. While the computational steps of stratification are relatively straightforward, the statistical concept of the pilot design is nuanced, and the process of stratifying a data set and interrogating the quality of that stratification can be thought-intensive. The stratamatch package is intended to make a prognostic score stratification pilot design easily accessible, and suggests several methods by which to diagnose the quality of a stratification scheme (e.g., Size-Ratio and Fisher-Mill plots). The overall goal of this effort is to push researchers toward approaches and diagnostics which emphasize strong study design in the observational setting.

Computational details

The results in this paper were obtained using R 3.6.2 with the stratamatch 0.1.3 package, dplyr-0.8.3, and glmnet 3.0. R itself and all packages used are available from the Comprehensive R Archive Network (CRAN) at https://CRAN.R-project.org/.

Acknowledgments

R.C.A. is funded by the National Institutes of Health (T32 LM 12409-2) and a Stanford Graduate Fellowship in Science and Engineering. J. H. C. is supported in part by the NIH Big Data 2 Knowledge initiative via the National Institute of Environmental Health Sciences under Award Number K01ES026837.

References

Aikens RC, Greaves D, Baiochi M (2019). “Using the Prognostic Score to Reduce Heterogeneity in Observational Studies.” 1908.09077.

Antonelli J, Cefalu M, Palmer N, Agniel D (2018). “Doubly Robust Matching Estimators for High Dimensional Confounding Adjustment.” Biometrics, 74(4), 1171–1179.

Chavez G, Richman IB, Kaimal R, Bentley J, Yasukawa LA, Altman RB, Periyakoil VS, Chen JH (2018). “Reversals and Limitations on High-Intensity, Life-Sustaining Treatments.” PloS one, 13(2), e0190569.

Friedman J, Hastie T, Tibshirani R (2001). The Elements of Statistical Learning, volume 1. Springer series in statistics New York.

Friedman J, Hastie T, Tibshirani R (2010). “Regularization Paths for Generalized Linear Models via Coordinate Descent.” Journal of Statistical Software, 33(1), 1–22. URL http://www.jstatsoft.org/v33/i01/.
Goodman SN, Schneeweiss S, Baiocchi M (2017). “Using Design Thinking to Differentiate Useful from Misleading Evidence in Observational Research.” *Jama*, **317**(7), 705–707.

Hansen BB (2008). “The Prognostic Analogue of the Propensity Score.” *Biometrika*, **95**(2), 481–488.

Hansen BB, Klopfer SO (2006). “Optimal Full Matching and Related Designs via Network Flows.” *Journal of Computational and Graphical Statistics*, **15**(3), 609–627.

Ho DE, Imai K, King G, Stuart EA, *et al.* (2011). “MatchIt: Nonparametric Preprocessing for Parametric Causal Inference.” *Journal of Statistical Software, http://gking. harvard. edu/matchit*.

King G, Nielsen R (2016). “Why Propensity Scores Should Not be Used for Matching.” Copy at *http://j. mp/1sexgVw Download Citation BibTex Tagged XML Download Paper, 378*.

Leacy FP, Stuart EA (2014). “On the Joint Use of Propensity and Prognostic Scores in Estimation of the Average Treatment Effect on the Treated: A Simulation Study.” *Statistics in medicine*, **33**(20), 3488–3508.

Pimentel SD, Yoon F, Keele L (2015). “Variable-Ratio Matching with Fine Balance in a Study of the Peer Health Exchange.” *Statistics in medicine*, **34**(30), 4070–4082.

Rosenbaum PR (1991). “A Characterization of Optimal Designs for Observational Studies.” *Journal of the Royal Statistical Society: Series B (Methodological)*, **53**(3), 597–610.

Rosenbaum PR (2005a). “Heterogeneity and Causality: Unit Heterogeneity and Design Sensitivity in Observational Studies.” *The American Statistician*, **59**(2), 147–152.

Rosenbaum PR (2005b). “Sensitivity Analysis in Observational Studies.” *Encyclopedia of statistics in behavioral science*, **4**, 1809–1814.

Rosenbaum PR, Rubin DB (1983). “The Central Role of the Propensity Score in Observational Studies for Causal Effects.” *Biometrika*, **70**(1), 41–55.

Rosenbaum PR, *et al.* (2010). *Design of Observational Studies*, volume 10. Springer.

Rubin DB, *et al.* (2008). “For Objective Causal Inference, Design Trumps Analysis.” *The Annals of Applied Statistics*, **2**(3), 808–840.
Affiliation:

Jonathan H. Chen
Center for Biomedical Informatics Research
and
Division of Hospital Medicine
Department of Medicine
Stanford University
Stanford, California, USA
E-mail: jonc101@stanford.edu
URL: http://healthrexlab.com/