Propensity Scoring matching in Cluster Randomized Trials

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BASS XIX
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Cluster Randomized Trial

Cluster randomized trials (CRTs): aims to evaluate the effects of interventions operated at the community level.
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Features of Group Randomized Trials:

- social units are selected as the units of randomization
- small sample size
- all clusters have to be available prior to study onset
Overview

- Propensity Scoring matching in Cluster Randomized Trials with Two Arms
  - Introduction and Motivating Examples
  - Propensity Score Matching
  - The BMW Design
  - Simulation study and Application

- Extension of BMW design to Clinical Trials with Three or More Arms

- Future Work
2. Propensity Scoring matching in Cluster Randomized Trials with Two Arms
**Introduction and Motivating Examples**

*INSTINCT Trial*: Aims to investigate the effectiveness of an education program in enhancing the tPA therapy use in stroke patients
**INTRODUCTION AND MOTIVATING EXAMPLES**

**INSTINCT Trial**: Aims to investigate the effectiveness of an education program in enhancing the tPA therapy use in stroke patients.

**Cluster-level Confounders**:

- baseline stroke volume (low vs. high) (*binary*)
- population density (urban vs. rural) (*binary*)
- percent male older than 65 (*continuous*)
- percent female older than 65 (*continuous*)
Propensity Score

Propensity Score: $\delta(x) = Pr(Z = 1 \mid X)$;

- Rosenbaum and Rubin (1984) Theorem 1: $x \perp z \mid \delta(x)$
- Implication: adjustment for the scalar propensity score is sufficient to remove bias due to all observed covariates
Propensity Score

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- Implication: adjustment for the scalar propensity score is sufficient to remove bias due to all observed covariates

- In non-randomized experiments: \( \delta(x) \) is unknown, sample estimate \( \hat{\delta}(x) \) can produce sample balance (Rosenbaum, 2002)

- In randomized clinical trials: \( \delta(x) \) is known, however, matching on \( \hat{\delta}(x) \) is still possible.
The BMW Design

- Applies optimal full matching with constraints technique to estimated propensity score
- Aims to minimizes the MSE of the treatment effect estimator
Propensity Score Matching in Observational Studies

- Set up a model for the exposure or treatment variable $Z$ to relate treatment to potential confounders $X$. For example:

$$\delta(x, \beta) = Pr(Z = 1 \mid X) = \frac{\exp(\beta' X)}{[1 + \exp(\beta' X)]}$$

- The estimated propensity score for the $i^{th}$ subject is

$$\hat{\delta}_i(x_i, \hat{\beta})$$
Similarity of covariates is measured through an estimated propensity score distance: Distance between $i$ and $j$: $d_{i,j} = |\hat{\delta}_i - \hat{\delta}_j|$

Matching assembles treated and control units as similar as possible into a same strata;
Propensity Score Matching

The quality of a particular matching is measured by:

\[
\Delta = \sum_{s=1}^{S} w(|T_s|, |C_s|) \cdot \frac{T_s \times C_s}{|T_s \times C_s|}
\]

where

\[
\frac{T_s \times C_s}{|T_s \times C_s|} = \sum_{(i,j) \in T_s \times C_s} \frac{|\hat{\delta}_i - \hat{\delta}_j|}{|T_s \times C_s|}
\]

is the average distance between the \(|T_s \times C_s|\) possible pairs in the s-th strata, and \(w(\cdot, \cdot)\) is a weight function.
Optimal Full Matching

- Full matching: $\min(|T_s|, |C_s|) = 1$, for $s = 1, 2, ..., S$. 
Optimal Full Matching

- **Full matching**: $\min(|T_s|, |C_s|) = 1$, for $s = 1, 2, \ldots, S$.

- Rosenbaum (1991, Lemma 2) showed that if the $w(\cdot, \cdot)$ in (1) is *neutral* or *favors small subclasses*, then there is always a full matching that is optimal.
  
  - *neutral or favors small subclass*:
    
    \[
    w(|T_s|, |C_s|) \geq w(|T_s| - 1, |C_s| - 1) + w(1, 1)
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  - neutral or favors small subclass:
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- Among the class of full matchings: \( w(|T_s|, |C_s|) = |T_s| + |C_s| - 1 \),
  \[
  \Delta = \sum_{s=1}^{S} (|T_s| + |C_s| - 1) \cdot T_s \times C_s = \sum_{s=1}^{S} \sum_{(i,j) \in T_s \times C_s} |\hat{\delta}_i - \hat{\delta}_j|.
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Optimal Full Matching with constraints

- Drawback of Full Matching: very unbalanced strata $\Rightarrow$ precision loss;
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- Remedy: Full Matching with Constraints $k$ (Hansen, 2004);
Optimal Full Matching with constraints

- Drawback of Full Matching: very unbalanced strata $\Rightarrow$ precision loss;

- Remedy: Full Matching with Constraints $k$ (Hansen, 2004);

- Find optimal full matching with constraint $k$:

$$\text{Minimize } \Delta = \sum_{s=1}^{S} \sum_{(i,j) \in T_s \times C_s} |\hat{\delta}_i - \hat{\delta}_j|$$

over the class of full matchings subject to $k^{-1} \leq |T_s|/|C_s| \leq k$. 
Model for Outcome

\[ Y_i = \alpha + \beta I(i \in T) + \sum_{j=1}^{r} \gamma_j X_{ij} + \varepsilon_i; \]
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- **Pooled Sample:** \( \hat{\beta}_{pool} = \bar{y}_T - \bar{y}_C \)

\[
\text{Bias}[\hat{\beta}_{pool} \mid T, C, X] = \sum_{j=1}^{r} \gamma_j (\bar{X}_{jT} - \bar{X}_{jC})
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\text{Var}[\hat{\beta}_{pool} \mid T, C, X] = \frac{2}{N} \sigma^2
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\text{Bias}[\hat{\beta}_{strata} \mid T, C, X] = \sum_{s=1}^{S} w_s \left( \sum_{j=1}^{r} \gamma_j (\bar{X}_{jT_s} - \bar{X}_{jC_s}) \right)
\]

\[
\text{Var}[\hat{\beta}_{strata} \mid T, C, X] = \sum_{s=1}^{S} w_s^2 \left( \frac{1}{|T_s|} + \frac{1}{|C_s|} \right) \sigma^2
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The BMW Design

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- **Step 4.** Repeat **Step 1** to **3** $M$ times; pick the randomized sample with minimum total distance $\Delta^*_k = \min(\Delta_{1k}, \Delta_{2k}, \ldots, \Delta_{Mk})$. 
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Choice of $k$ ($k = 1, 2, ..., \frac{N}{2} - 1$):
The BMW Design (cont’d): choices of $k$ and $M$

- Choice of $k$ ($k = 1, 2, \ldots, \frac{N}{2} - 1$):
  - If $\gamma$ is known and $M$ is fixed,
    
    **Step 5.** Compute MSE based on the randomization with $\Delta_k^*$, then repeat step 1 to 4 for all choices of $k$ to find the optimal $k^*$ s.t. $MSE_{k^*} = \min(MSE_1^*, MSE_2^*, \ldots, MSE_{\frac{N}{2} - 1}^*)$. 

The BMW Design (cont’d): choices of $k$ and $M$

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  - If $\gamma$ is unknown,
    - Simulation study suggests that $k = 2$ is a suitable choice under most of the confounding scenarios;

- Choice of $M$: $M \in [10, 20]$ suggested by simulation study;
One possible model-based approach suggested by an AE:

\[ Y_i = \alpha + \beta I(i \in T) + \gamma \hat{\delta}_i + \varepsilon_i. \]
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\[ Y_i = \alpha + \beta I(i \in T) + \gamma \delta_i + \varepsilon_i. \]

- if the propensity score model is appropriately specified:
  - True model: \[ Y_i = \alpha + \beta I(i \in T) + \gamma_1 X_i + \gamma_2 X_i^2 + \varepsilon_i \]
  - Specified Model:
    \[ \logit(\delta_i) = \logit(Pr(Z = 1 \mid X_i; \alpha)) = \alpha_1 + \alpha_2 X_i + \alpha_3 X_i^2, \]
One possible **model-based approach** suggested by an AE:

\[ Y_i = \alpha + \beta I(i \in T) + \gamma \hat{\delta}_i + \varepsilon_i. \]

- if the propensity score model is **appropriately** specified:
  - True model: \( Y_i = \alpha + \beta I(i \in T) + \gamma_1 X_i + \gamma_2 X_i^2 + \varepsilon_i \)
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- if the propensity score model is **inappropriately** specified:
  - \( \logit(\delta_i) = \logit(Pr(Z = 1 | X_i; \alpha)) = \alpha_1 + \alpha_2 X_i. \)
Robins-Mark-Newey (1992) consistent E-estimator $\tilde{\beta}_E$:

$$\tilde{\beta}_E = \sum_{i=1}^{n} \frac{Y_i(Z_i - \hat{\delta}_i)}{Z_i(Z_i - \hat{\delta}_i)}.$$

$\tilde{\beta}_E$ is consistent when the model for propensity score $\hat{\delta}_i$ is **correctly** specified. The E-estimation procedure is designed for the observational studies.
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- Our simulation study suggests that the BMW approach is more efficient and robust than the E-estimator.
Greevy et al. (2004) suggest multivariate matching design based on Mahalanobis distance:

- Form optimal nonbipartite matching on the multivariate Mahalanobis distance;
- Randomly assign treatments within each pair;
**Greevy et al.** (2004) suggest multivariate matching design based on Mahalanobis distance:

- Form **optimal nonbipartite matching** on the multivariate Mahalanobis distance;
- Randomly assign treatments within each pair;
- As the confounding effects increase or the number of covariates increase, the BMW design becomes much more effective than Greevy’s design in reducing MSE.
Simulation Study

- generating response: $Y_i = \beta Z_i + \sum_{j=1}^{r} \gamma_j X_{ij} + \varepsilon_i$

- true treatment effect: $\beta = 0.7$

- true confounding effects: $\gamma_j = \gamma, \ j = 1, \ldots, r$ where $\gamma = 0.5, 1.0, 1.5, 2.0$

- covariate setting:
  - $X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5)$
  - $X_1, X_2 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5); X_3, X_4 \overset{i.i.d}{\sim} \text{N}(0, 0.25)$
  - $X_1, X_2 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5); X_3, X_4 \overset{i.i.d}{\sim} \text{Bernoulli}(0.66)$
  - $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5)$
Simulation Study: Competing Designs

The BMW design versus:

- Completely Randomized Design;
- Matched-Pair Design;
- Model-based Approach;
- Robins-Mark-Newey’s E-estimator $\tilde{\beta}_E$;
- Greevy et al. multivariate matching design on Mahalanobis distance;
## Percent Reduction in MSE

Covariate Setting: $X_1, X_2, X_3, X_4 \overset{i.i.d.}{\sim} \text{Bernoulli}(0.5)$

<table>
<thead>
<tr>
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- Confounding Effects $\gamma$;
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- Confounding Effects $\gamma$;
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- Replication $M$: $M = 10$;
## Percent Reduction in MSE

- **Effects of Covariate Settings:**

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</table>

### \( X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.5) \)

<table>
<thead>
<tr>
<th>( (1.0,1.0,1.0,1.0) )</th>
<th>5</th>
<th>35.6</th>
<th>43.5</th>
<th>39.6</th>
<th>24.5</th>
<th>33.9</th>
<th>29.3</th>
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<td></td>
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<td>44.4</td>
<td>41.7</td>
<td>30.1</td>
<td>34.9</td>
<td>31.7</td>
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<td>48.6</td>
<td>46.2</td>
<td>41.8</td>
<td>39.8</td>
<td>36.9</td>
</tr>
</tbody>
</table>

### \( X_1, X_2 \overset{i.i.d}{\sim} Bernoulli(0.5); X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.66) \)

<table>
<thead>
<tr>
<th>( (1.0,1.0,1.0,1.0) )</th>
<th>5</th>
<th>32.2</th>
<th>40.7</th>
<th>36.7</th>
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<th>26.2</th>
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<tbody>
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<td></td>
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<td>37.9</td>
<td>43.1</td>
<td>39.3</td>
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<td>33.7</td>
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<td>41.8</td>
<td>44.1</td>
<td>41.2</td>
<td>32.2</td>
<td>34.8</td>
<td>31.4</td>
</tr>
</tbody>
</table>

### \( X_1, X_2 \overset{i.i.d}{\sim} Bernoulli(0.5); X_3, X_4 \overset{i.i.d}{\sim} N(0, 0.25) \)

<table>
<thead>
<tr>
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<th>24.3</th>
<th>30.7</th>
<th>27.2</th>
<th>13.2</th>
<th>20.5</th>
<th>16.5</th>
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<tbody>
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<td>32.4</td>
<td>29.1</td>
<td>18.3</td>
<td>22.4</td>
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<tr>
<td></td>
<td>20</td>
<td>32.8</td>
<td>33.0</td>
<td>30.1</td>
<td>22.9</td>
<td>23.2</td>
<td>19.8</td>
</tr>
</tbody>
</table>

### \( X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 \overset{i.i.d}{\sim} Bernoulli(0.5) \)

<table>
<thead>
<tr>
<th>( (1.0,1.0,1.0,1.0, ), 1.0,1.0,1.0,1.0 )</th>
<th>5</th>
<th>28.7</th>
<th>52.4</th>
<th>52.2</th>
<th>23.3</th>
<th>48.8</th>
<th>48.6</th>
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<tr>
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<td>35.8</td>
<td>56.1</td>
<td>53.1</td>
<td>30.9</td>
<td>52.8</td>
<td>49.5</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>43.2</td>
<td>57.6</td>
<td>54.2</td>
<td>38.9</td>
<td>54.4</td>
<td>50.7</td>
</tr>
</tbody>
</table>
## Percent Reduction in MSE

- **BMW vs. model-based approach:**

<table>
<thead>
<tr>
<th>$\gamma$</th>
<th>$M$</th>
<th>$MSE_{(MB)}$</th>
<th>$MSE$ Percent Reduction(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$BMW$ vs. $MB$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>$k = 1$</td>
</tr>
</tbody>
</table>

where propensity score **inappropriately** specified (17) (18)

\[ X \sim_{i.i.d} \text{Normal}(0, 0.25) \]

- (0.5, 0.5) 10 0.185 0.65 14.75 12.25
- (1.0, 1.0) 10 0.365 -0.15 30.03 32.31
- (1.5, 1.5) 10 0.665 5.80 41.88 46.12

where propensity score **appropriately** specified (15) (16)

\[ X_1, X_2, X_3, X_4 \sim_{i.i.d} \text{Bernoulli}(0.5) \]

- (0.5,0.5,0.5,0.5) 10 0.165 15.01 15.74 6.79
- (1.0,1.0,1.0,1.0) 10 0.166 -0.87 6.02 1.44
- (1.5,1.5,1.5,1.5) 10 0.166 -29.84 -2.49 -11.31
### Percent Reduction in MSE

- BMW vs. Robins-Mark-Newey E-estimator:

<table>
<thead>
<tr>
<th>( \gamma )</th>
<th>( M )</th>
<th>MSE (( E - \text{est} ))</th>
<th>MSE Percent Reduction(%)(BMW vs. ( E - \text{est} ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>( k = 1 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( k = 2 )</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( k = 3 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

where propensity score \textit{inappropriately} specified (17) (18)

[\( X \overset{i.i.d.}{\sim} \text{Normal}(0, 0.25) \)]

- (0.5, 0.5) 10 0.334 | 45.06 | 52.85 | 51.47
- (1.0, 1.0) 10 0.964 | 62.10 | 73.52 | 74.39
- (1.5, 1.5) 10 2.013 | 68.90 | 80.81 | **82.21**

where propensity score \textit{appropriately} specified (15) (16)

[\( X_1, X_2, X_3, X_4 \overset{i.i.d.}{\sim} \text{Bernoulli}(0.5) \)]

- (0.5, 0.5, 0.5, 0.5) 10 0.211 | 33.41 | 33.98 | 26.97
- (1.0, 1.0, 1.0, 1.0) 10 0.528 | 68.38 | 70.54 | 69.10
- (1.5, 1.5, 1.5, 1.5) 10 0.971 | 77.85 | 82.52 | **81.01**
## Percent Reduction in MSE

- **BMW vs. multivariate non-bipartite matching design:**

<table>
<thead>
<tr>
<th>γ</th>
<th>( \sum_{j=1}^{8} \gamma_j )</th>
<th>( M )</th>
<th>( MSE ) (NB Design)</th>
<th>( MSE ) (BMW vs. NB Design)</th>
<th>( \text{Percent Reduction}(%) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>( k = 1 )</td>
<td>( k = 2 )</td>
<td>( k = 3 )</td>
</tr>
</tbody>
</table>

\[ X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5) \]

|         | 5                | 2.42   | 4.49                   | 8.53                       |
|         | (1,0,1.0,1.0,1.0) |        |                        |                            |
|         | 4                | 0.185  | 9.62                   | 15.79                      | 11.68                           |
|         | 20               | 24.78  | 22.18                  | 18.44                      |

\[ X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5) \]

|         | 5                | -25.19 | 16.39                  | 16.07                      |
|         | (1,0,1.0,1.0,1.0,1.0,1.0,1.0) |        |                        |                            |
|         | 8                | 0.222  | -12.76                 | 22.92                      | 17.65                           |
|         | 20               | 0.26   | 25.53                  | 19.59                      |
Application to Instinct Trial

- Cluster-level confounders:
  - Stroke Volume;
  - Population Density;
  - Percent male greater than 65;
  - Percent Female greater than 65;
Application to Instinct Trial

- Cluster-level confounders:
  - Stroke Volume;
  - Population Density;
  - Percent male greater than 65;
  - Percent Female greater than 65;

Application to Instinct Trial

- Cluster-level confounders:
  - Stroke Volume;
  - Population Density;
  - Percent male greater than 65;
  - Percent Female greater than 65;


- BMW Design:
  - When $\gamma_j'$s are unknown: $k = 2; M = 10;$
### Application to Instinct Trial: BMW results

<table>
<thead>
<tr>
<th>Strata</th>
<th>( ID(\hat{\delta}) )</th>
<th>( X_1 )</th>
<th>( X_2 )</th>
<th>( X_3 )</th>
<th>( X_4 )</th>
<th>( ID(\hat{\delta}) )</th>
<th>( X_1 )</th>
<th>( X_2 )</th>
<th>( X_3 )</th>
<th>( X_4 )</th>
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<tbody>
<tr>
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<td>0.13</td>
<td>0</td>
<td>0</td>
<td>6 (0.35)</td>
<td>0.19</td>
<td>0.07</td>
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<td>0</td>
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<tr>
<td>2</td>
<td>2 (0.38)</td>
<td>0.17</td>
<td>0.11</td>
<td>1</td>
<td>0</td>
<td>8 (0.35)</td>
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<td>0.14</td>
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<td>11 (0.40)</td>
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<tr>
<td>3</td>
<td>3 (0.63)</td>
<td>0.13</td>
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<td>1</td>
<td>1</td>
<td>9 (0.63)</td>
<td>0.14</td>
<td>0.06</td>
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<td></td>
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<td></td>
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<td>19 (0.67)</td>
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<tr>
<td>4</td>
<td>4 (0.58)</td>
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<td>12 (0.60)</td>
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<td>5</td>
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<td>13 (0.32)</td>
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<td>15 (0.31)</td>
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<td>6</td>
<td>17 (0.41)</td>
<td>0.24</td>
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<td>10 (0.41)</td>
<td>0.26</td>
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<td>22 (0.43)</td>
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<td>0.06</td>
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<td>1</td>
<td>16 (0.61)</td>
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<td>0.07</td>
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<tr>
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<td>21 (0.60)</td>
<td>0.18</td>
<td>0.14</td>
<td>0</td>
<td>1</td>
<td>5 (0.61)</td>
<td>0.19</td>
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<td>0</td>
<td>1</td>
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<tr>
<td>9</td>
<td>24 (0.62)</td>
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<td>0.16</td>
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<td>7 (0.62)</td>
<td>0.24</td>
<td>0.19</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>23 (0.62)</td>
<td>0.11</td>
<td>0.07</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Discussion

- BMW design reduces the chance imbalance on observed covariates and retains random assignment to balance on average over unobserved;

- The design is flexible to choose other criteria besides MSE to trade-off bias and variance;

- Carefully chosen $M$:
  - The larger $M$ is, the better balance BMW can attain; $M = 100$ and $k = 1$ is recommended;
  - If $M$ is too large ($M$ close to $\left(\frac{N}{2}\right)$), e.g. $M = \infty$ and $k = 1$, the BMW design always lead to the same set of matched pair with same treatment assignment for continuous covariates;

- Advantages of BMW design over model based covariate adjustment approach:
  - Simple;
  - Performs well for small studies: does not require a valid model of the covariate effects.
Two major areas of Generalization:

- Cluster Randomized Trials with more than two arms;
- Clinical Trials with Staggered Entry – Adaptive Randomization Design;
3. Extension to CRT with Three or More Arms

- Cluster Randomized Trial
- Overview
- Matching
- BMW Design
- True Optimum
- Discussion

4. Future

5. References
For three groups:

\[ A = \{ \eta_A^1, ..., \eta_A^{N/3} \}, \quad B = \{ \eta_B^1, ..., \eta_B^{N/3} \}, \quad C = \{ \eta_C^1, ..., \eta_C^{N/3} \} \]
Propensity Score

- For three groups:
  \( A = \{\eta_A^1, ..., \eta_A^{N/3}\}, \ B = \{\eta_B^1, ..., \eta_B^{N/3}\}, \ C = \{\eta_C^1, ..., \eta_C^{N/3}\} \):

- Baseline category model to relates treatment to confounders:

  \[
  \delta_{t,i} = Pr(Z = t \mid X_i; \alpha_t) = \frac{\exp\{\alpha_t X_i^T\}}{1+\exp\{\alpha_1 X_i^T\}+\exp\{\alpha_2 X_i^T\}}
  \]

  where \( t = 1, 2, 3 \) with \( \alpha_3 = 0 \).
Propensity Score

- For three groups:
  \[ A = \{\eta_1^A, \ldots, \eta_{N/3}^A\}, \quad B = \{\eta_1^B, \ldots, \eta_{N/3}^B\}, \quad C = \{\eta_1^C, \ldots, \eta_{N/3}^C\} : \]

- Baseline category model to relates treatment to confounders:

  \[
  \delta_{t,i} = Pr(Z = t \mid X_i; \alpha_t) = \frac{\exp\{\alpha_t X_i^T\}}{1 + \exp\{\alpha_1 X_i^T\} + \exp\{\alpha_2 X_i^T\}}
  \]

  where \( t = 1, 2, 3 \) with \( \alpha_3 = 0 \).

- The estimated propensity score for the \( i^{th} \) subject is

  \[
  (\hat{\delta}_{1,i}, \hat{\delta}_{2,i}, \hat{\delta}_{3,i})
  \]
Propensity Score

- For three groups:
  \[ A = \{ \eta_1^A, ..., \eta_{N/3}^A \}, \quad B = \{ \eta_1^B, ..., \eta_{N/3}^B \}, \quad C = \{ \eta_1^C, ..., \eta_{N/3}^C \} \]

- Baseline category model to relates treatment to confounders:
  \[
  \delta_{t,i} = Pr(Z = t \mid X_i; \alpha_t) = \exp\{\alpha_t X_i^T\}/\{1+\exp\{\alpha_1 X_i^T\}+\exp\{\alpha_2 X_i^T\}\} 
  \]
  where \( t = 1, 2, 3 \) with \( \alpha_3 = 0 \).

- The estimated propensity score for the \( i^{th} \) subject is
  \[
  (\hat{\delta}_{1,i}, \hat{\delta}_{2,i}, \hat{\delta}_{3,i}) 
  \]

- Similarity of covariates is measured through an estimated Euclidean distance:
  \[
  \delta\{ (\eta_i^A, \eta_j^B) \} = \sqrt{(\hat{\delta}_1^A - \hat{\delta}_1^B)^2 + (\hat{\delta}_2^A - \hat{\delta}_2^B)^2 + (\hat{\delta}_3^A - \hat{\delta}_3^B)^2} 
  \]
Optimal tripartite matching

How to optimally match on three groups?
Optimal tripartite matching

How to optimally match on three groups?

- Ad hoc approaches which may not lead to the optimal matching, but to the solutions that are close to optimal were developed.
Optimal tripartite matching

How to optimally match on three groups?

- The Optimal tripartite matching problem: NP complete problem;

- Ad hoc approaches which may not lead to the optimal matching, but to the solutions that are close to optimal were developed.
Optimal tripartite matching

How to optimally match on three groups?

- The Optimal tripartite matching problem: NP complete problem;

- Given group Size $m$, number of comparisons $= (m!)^2$;
  - Group Size $m = 3$, number of comparisons $= 36$;
  - Group Size $m = 4$, number of comparisons $= 576$;
  - Group Size $m = 5$, number of comparisons $= 14400$;
  - Group Size $m = 6$, number of comparisons $= 518400$;
  - Group Size $m = 10$, number of comparisons $= 1.316819e^{13}$;
Optimal tripartite matching

How to optimally match on three groups?

- The Optimal tripartite matching problem: NP complete problem;
- Given group Size $m$, number of comparisons $= (m!)^2$;
  - Group Size $m = 3$, number of comparisons $= 36$;
  - Group Size $m = 4$, number of comparisons $= 576$;
  - Group Size $m = 5$, number of comparisons $= 14400$;
  - Group Size $m = 6$, number of comparisons $= 518400$;
  - Group Size $m = 10$, number of comparisons $= 1.316819e^{13}$;
- Ad hoc approaches which may not lead to the optimal matching, but to the solutions that are close to optimal were developed.
Bo and Rosenbaum (2004): $P$ is an optimal non-bipartite matching with $\Delta(P) < +\infty$ if and only if $P$ is also an optimal, feasible tripartite matching.
Bo and Rosenbaum (2004): $P$ is an optimal non-bipartite matching with $\Delta(P) < +\infty$ if and only if $P$ is also an optimal, feasible tripartite matching.

- Given a single set
  $\Theta = \mathcal{A} \cup \mathcal{B} \cup \mathcal{C} = (\eta_1^A, ..., \eta_{N/3}^A, \eta_1^B, ..., \eta_{N/3}^B, \eta_1^C, ..., \eta_{N/3}^C);$ 

- \[
  \delta\{(\eta_i^m, \eta_j^n)\} = \begin{cases} 
    \sqrt{(\hat{\delta}_{1,i}^m - \hat{\delta}_{1,j}^n)^2 + (\hat{\delta}_{2,i}^m - \hat{\delta}_{2,j}^n)^2 + (\hat{\delta}_{3,i}^m - \hat{\delta}_{3,j}^n)^2} & \text{if } m \neq n; \\
    +\infty & \text{if } m = n. 
  \end{cases}
\]

- Find the optimal non-bipartite matching;
Ad Hoc Method (I). Incomplete Block Design with Disjoint Pairs

How to obtain incomplete block of disjoint pairs through optimal nonbipartite matching?
Ad Hoc Method (II). Symmetric Tripartite Matching With Triples

- $\Delta^{*}_{M_A} = \Delta^{*}_{M_{A,C}} + \Delta^{*}_{M_{A,B}} + \sum_{\omega \in M^+_{B,C}} \delta(\omega)$
- $\Delta^{*}_{M_B} = \Delta^{*}_{M_{A,B}} + \Delta^{*}_{M_{B,C}} + \sum_{\omega \in M^+_{A,C}} \delta(\omega)$
- $\Delta^{*}_{M_C} = \Delta^{*}_{M_{B,C}} + \Delta^{*}_{M_{A,C}} + \sum_{\omega \in M^+_{A,B}} \delta(\omega)$
- *optimal reference group:
  $\Delta^{*}_{M_{A,B,C}} = \min(\Delta^{*}_{M_A}, \Delta^{*}_{M_B}, \Delta^{*}_{M_C})$
Ad Hoc Method (II). Symmetric Tripartite Matching With Triples

- $\Delta^*_{M_A} = \Delta^*_{M_{A,C}} + \Delta^*_{M_{A,B}} + \sum_{\omega \in M^+_{B,C}} \delta(\omega)$
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- $\Delta^*_{M_C} = \Delta^*_{M_{B,C}} + \Delta^*_{M_{A,C}} + \sum_{\omega \in M^+_{A,B}} \delta(\omega)$
- *optimal reference group*:
  $\Delta^*_{M_{A,B,C}} = \min(\Delta^*_{M_A}, \Delta^*_{M_B}, \Delta^*_{M_C})$
Ad Hoc Method (II). Symmetric Tripartite Matching With Triples

- $\Delta^*_{M_A} = \Delta^*_{M_{A,C}} + \Delta^*_{M_{A,B}} + \sum_{\omega \in M^+_{B,C}} \delta(\omega)$
- $\Delta^*_{M_B} = \Delta^*_{M_{A,B}} + \Delta^*_{M_{B,C}} + \sum_{\omega \in M^+_{A,C}} \delta(\omega)$
- $\Delta^*_{M_C} = \Delta^*_{M_{B,C}} + \Delta^*_{M_{A,C}} + \sum_{\omega \in M^+_{A,B}} \delta(\omega)$
- **optimal reference group:**
  $\Delta^*_{M_{A,B,C}} = \min(\Delta^*_{M_A}, \Delta^*_{M_B}, \Delta^*_{M_C})$
Ad Hoc Method (III). Asymmetric Tripartite Matching With Triples

- With group $B$ as predefined reference group:
- $\Delta_B^* = \Delta_{M_{A,B}}^* + \Delta_{M_{B,C}}^*$
- $\sum_{\omega \in M_{A,C}^+} \delta(\omega)$ is not taken into account;
Model: \[ Y_i = \alpha + \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma^T X_i + \varepsilon_i \]
The BMW Design with Three Arms: Assessment Model

Model: $Y_i = \alpha + \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma^T X_i + \varepsilon_i$

- Pooled Samples:

$$\hat{\beta}_{1,\text{pool}} = \bar{y}_A - \bar{y}_C;$$

$$MSE(\hat{\beta}_{1,\text{pool}}) = \frac{6}{N} \gamma^T \Sigma \gamma + \frac{6}{N} \sigma^2$$
The BMW Design with Three Arms: Assessment Model

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$$MSE(\hat{\beta}_1^{ICB}) = \frac{1}{9} \gamma^T \text{Cov}^* \left[2(\overline{X}_{A13} - \overline{X}_{C13}) + (\overline{X}_{A12} - \overline{X}_{B12}) + (\overline{X}_{B23} - \overline{X}_{C23})\right] \gamma + 8\sigma^2 / N$$
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  \]
  \[
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  \]

- **Matched Samples (ATM and STM Design):**
  \[
  \hat{\beta}_{1,\text{ATM}} = \hat{\beta}_{1,\text{STM}} = \overline{y}_A - \overline{y}_C
  \]
  \[
  MSE(\hat{\beta}_{1,\text{STM}}) = \gamma^T \text{Cov}^{**} (\overline{X}_A - \overline{X}_C) \gamma + 6\sigma^2 / N.
  \]
The BMW Design with Three Arms: Algorithm

The design for three-arms trials with specified parameter $M$: 
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- **Step 1.** Randomize $1/3$, $1/3$ and $1/3$ of the subjects to the treatment groups $A$, $B$ and $C$, respectively;
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  - symmetric tripartite matching design.

Record the minimum total distance $\Delta$ for the given randomization.
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- **Step 4.** Repeat Steps 1 to 3 for $M$ times and choose the randomization with minimum total distance $\Delta^* = \min(\Delta_1, \Delta_2, ..., \Delta_M)$. 
Simulation Study

- generating response:
  \[ Y_i = \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma^T X_i + \varepsilon_i, \quad i = 1, 2, \ldots, N \]

- true treatment effect: \( \beta_1 = \beta_2 = 0.5 \)

- true confounding effects: \( \gamma_j = \gamma, \quad j = 1, \ldots, r, \) where \( \gamma = 0.5, 1.0, 1.5 \)

- covariate setting:
  - \( X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5) \)
  - \( X_1, X_2 \overset{i.i.d}{\sim} \text{Bernoulli}(0.5); \) \( X_3, X_4 \overset{i.i.d}{\sim} \mathcal{N}(0, 0.25) \)

- We consider sample sizes \( N = 24 \) or \( 36 \);
The BMW Design with Three Arms: Simulation Results \( N = 24 \)

<table>
<thead>
<tr>
<th>( \gamma )</th>
<th>( M )</th>
<th>( MSE ) ((CR)) ((ICB \ vs. \ CR \ Design))</th>
<th>( MSE ) (% ) ((STM \ vs. \ CR \ Design))</th>
<th>( MSE ) (% ) ((ATM \ vs. \ CR \ Design))</th>
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<td>1.5</td>
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<td>0.806</td>
<td>40.20</td>
<td>53.61</td>
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<tr>
<td>( X_1, X_2, X_3, X_4 ) (i.i.d) (Bernoulli(0.5))</td>
<td></td>
<td></td>
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</tbody>
</table>

\[ \hat{\beta}_1 = \hat{\beta}_{AC} \]
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\[ \hat{\beta}_1 \ or \ \hat{\beta}_2 \]
\[ \hat{\beta}_{AB} = \hat{\beta}_1 - \hat{\beta}_2 \]

\[ X_1, X_2, X_3, X_4 \] \(i.i.d\) \(Bernoulli(0.5)\); \(X_1, X_2 \) \(i.i.d\) \(Bernoulli(0.5)\); \(X_3, X_4 \) \(i.i.d\) \(N(0, 0.25)\)

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</tr>
</thead>
<tbody>
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<tr>
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<tr>
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<td>0.600</td>
<td>29.24</td>
<td>44.37</td>
</tr>
<tr>
<td>( X_1, X_2 ) (i.i.d) (Bernoulli(0.5)); (X_3, X_4 ) (i.i.d) (N(0, 0.25))</td>
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Comparison to the True Optimum

How close the proposed symmetric tripartite matching is to the true optimal tripartite matching method?
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- **Model:**

  \[ Y_i = \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma X_i + \varepsilon_i, \quad i = 1, 2, \ldots, 18 \]

  where \( X_i \overset{i.i.d.}{\sim} \mathcal{N}(0, 0.25) \) and \( \varepsilon_i \overset{i.i.d.}{\sim} \mathcal{N}(0, 1) \) and \( N = 3 \times 6 = 18 \)
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- **Algorithm:** Dynamic programming algorithm;
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- **Algorithm**: Dynamic programming algorithm;

- **Results**: The symmetric tripartite matching algorithm is nearly optimal:
  - Difference in minimum Euclidean Distances;
  - MSE of treatment effect estimator;
Discussion

- The 3-arms BMW design can be further extended to be used in 4-arms or larger trials, e.g. 2x2 factorial design;
  - The symmetric quadripartite matching; √
  - The asymmetric quadripartite matching; √
  - Method of finding Optimal balanced incomplete block design through nonbipartite matching; ×

- Limitation: The BMW design may not perform well in the studies with very small sample size (e.g. group size < 10 and number of covariates ≥ 4);
  - The propensity score model may not work well due to the complete separation of cases and controls by covariates;
  - One might drop less important covariates;
Future Work in Personalized Medicine
Personalized Medicine Trials Design: Biomarker-stratified Design

N=200 Patients
Personalized Medicine Trials Design: Biomarker-stratified Design
Personalized Medicine Trials Design: Biomarker-stratified Design

N=200 Patients

Biomarker 1

+ N=110
  \[\text{M2} \quad \text{M2}\]

- N=90
  \[\text{M2} \quad \text{M2}\]

N=60
N=50
N=44
N=46
Personalized Medicine Trials Design: Biomarker-stratified Design

N=200 Patients

Biomarker 1

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Biomarker 1

M2 M2

+ N=60 - N=50

M3 M3

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M3 M3

+ N=22 - N=20 + N=23 - N=23

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References
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