Propensity Scoring matching in Cluster Randomized Trials

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Cluster Randomized Trial

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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

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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

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- 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:

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

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

$$\hat{\delta}_i(x_i, \hat{\beta})$$

Propensity Score Matching

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:

$$\Delta = \sum_{s=1}^{S} w(|T_s|, |C_s|) \bullet \overline{T_s \times C_s}$$

where

$$\overline{T_s \times C_s} = \sum_{(i,j) \in T_s \times C_s} |\widehat{\delta}_i - \widehat{\delta}_j| / |T_s \times C_s|$$

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

Optimal Full Matching

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  - *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:*
    $w(|T_s|, |C_s|) \geq w(|T_s| - 1, |C_s| - 1) + w(1, 1)$

- Among the class of full matchings: $w(|T_s|, |C_s|) = |T_s| + |C_s| - 1$,

$$\Delta = \sum_{s=1}^{S} (|T_s| + |C_s| - 1) \bullet \overline{T_s \times C_s} = \sum_{s=1}^{S} \sum_{(i,j) \in T_s \times C_s} |\widehat{\delta}_i - \widehat{\delta}_j|.$$

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- Remedy: Full Matching with Constraints k(Hansen, 2004);
- Find optimal full matching with constraint k:

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

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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  Bias[$\hat{\beta}_{pool} \mid T, C, X$] = $\sum_{j=1}^{r} \gamma_j (\bar{X}_{jT} - \bar{X}_{jC})$

  Var[$\hat{\beta}_{pool} \mid T, C, X$] = $\frac{2}{N}\sigma^2$

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- *Step 4.* Repeat *Step* 1 to 3 M times; pick the randomized sample with minimum total distance $\Delta_k^* = \min(\Delta_{1k}, \Delta_{2k}, ..., \Delta_{Mk})$.

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  - If γ is known and M is fixed,

    Step 5. Compute MSE based on the randomization with Δ_k^*, then repeat *step* 1 to 4 for all choices of k to find the optimal k^* s.t. $MSE_{k^*} = \min(MSE_1^*, MSE_2^*, ..., MSE_{\frac{N}{2}-1}^*)$.

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- Choice of k ($k = 1, 2, ..., \frac{N}{2} - 1$):
  - If γ is known and M is fixed,

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  - If γ 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;

Alternative Approaches I

One possible model-based approach suggested by an AE:

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  - True model: $Y_i = \alpha + \beta I(i \in T) + \gamma_1 X_i + \gamma_2 X_i^2 + \varepsilon_i$
  - Specified Model:
    $\text{logit}(\delta_i) = \text{logit}(Pr(Z = 1 \mid X_i; \alpha)) = \alpha_1 + \alpha_2 X_i + \alpha_3 X_i^2,$

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    $\text{logit}(\delta_i) = \text{logit}(Pr(Z = 1 \mid X_i; \alpha)) = \alpha_1 + \alpha_2 X_i + \alpha_3 X_i^2,$
- if the propensity score model is *inappropriately* specified:
  - $\text{logit}(\delta_i) = \text{logit}(Pr(Z = 1 \mid X_i; \alpha)) = \alpha_1 + \alpha_2 X_i.$

Alternative Approaches II

Robins-Mark-Newey (1992) consistent E-estimator $\widetilde{\beta_E}$:

$$\widetilde{\beta_E} = \sum_{i=1}^{n} Y_i(Z_i - \widehat{\delta}_i) \; / \; \sum_{i=1}^{n} Z_i(Z_i - \widehat{\delta}_i).$$

$\widetilde{\beta_E}$ is consistent when the model for propensity score $\widehat{\delta}_i$ is *correctly* specified.
The E-estimation procedure is designed for the observational studies.

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The E-estimation procedure is designed for the observational studies.

- Our simulation study suggests that the BMW approach is more efficient and robust than the E-estimator.

Alternative Approaches III

Greevy et al.(2004) suggest multivariate matching design based on Mahalanobis distance:

- Form optimal nonbipartite matching on the multivariate Mahalanobis distance;
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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: $\gamma_j = \gamma,\ j = 1, ..., r$ where $\gamma = 0.5,\ 1.0,\ 1.5,\ 2.0$
- covariate setting:
  - $X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim}$ Bernoulli(0.5);
  - $X_1, X_2 \overset{i.i.d}{\sim}$ Bernoulli(0.5); $X_3, X_4 \overset{i.i.d}{\sim} N(0, 0.25)$;
  - $X_1, X_2 \overset{i.i.d}{\sim}$ Bernoulli(0.5); $X_3, X_4 \overset{i.i.d}{\sim}$ Bernoulli(0.66).
  - $X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 \overset{i.i.d}{\sim}$ 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 $\widetilde{\beta_E}$;
- Greevy et al. multivariate matching design on Mahalanobis distance;

Percent Reduction in MSE

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

γ_j	M	(BMW vs. CR Design)			(BMW vs. MP Design)		
		$k=1$	$k=2$	$k=3$	$k=1$	$k=2$	$k=3$
(0.5, 0.5, 0.5, 0.5)	5	12.2	10.3	6.8	7.9	5.9	2.3
	10	14.4	11.7	7.1	10.2	7.5	2.6
	20	17.4	13.5	8.8	13.4	9.3	4.4
(1.0, 1.0, 1.0, 1.0)	5	35.6	43.5	39.6	24.5	33.9	29.3
	10	40.3	44.4	41.7	30.1	34.9	31.7
	20	50.3	48.6	46.2	41.8	39.8	36.9
(2.0, 2.0, 2.0, 2.0)	5	54.5	72.2	69.0	39.8	63.2	59.0
	10	61.4	73.7	70.3	49.0	65.3	60.8
	20	68.5	74.1	71.4	58.5	65.7	62.3

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- Confounding Effects γ;

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- Confounding Effects γ;
- Constraint k: $k = 2$;

Percent Reduction in MSE

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- Confounding Effects γ;
- Constraint k: $k = 2$;
- Replication M: $M = 10$:

Percent Reduction in MSE

- Effects of Covariate Settings:

γ_j	M	(BMW vs. CR Design)			(BMW vs. MP Design)		
		$k=1$	$k=2$	$k=3$	$k=1$	$k=2$	$k=3$
$X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.5)$							
(1.0,1.0,1.0,1.0)	5	35.6	43.5	39.6	24.5	33.9	29.3
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	20	50.3	48.6	46.2	41.8	39.8	36.9
$X_1, X_2 \overset{i.i.d}{\sim} Bernoulli(0.5); X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.66)$							
(1.0,1.0,1.0,1.0)	5	32.2	40.7	36.7	20.9	30.9	26.2
	10	37.9	43.1	39.3	27.6	33.7	29.3
	20	41.8	44.1	41.2	32.2	34.8	31.4
$X_1, X_2 \overset{i.i.d}{\sim} Bernoulli(0.5); X_3, X_4 \overset{i.i.d}{\sim} N(0, 0.25)$							
(1.0,1.0,1.0,1.0)	5	24.3	30.7	27.2	13.2	20.5	16.5
	10	28.8	32.4	29.1	18.3	22.4	18.7
	20	32.8	33.0	30.1	22.9	23.2	19.8
$X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 \overset{i.i.d}{\sim} Bernoulli(0.5)$							
(1.0,1.0,1.0,1.0, 1.0,1.0,1.0,1.0)	5	28.7	52.4	52.2	23.3	48.8	48.6
	10	35.8	56.1	53.1	30.9	52.8	49.5
	20	43.2	57.6	54.2	38.9	54.4	50.7

Percent Reduction in MSE

- BMW vs. model-based approach:

γ	M	MSE (MB)	MSE Percent Reduction(%) (BMW vs. MB)		
			$k=1$	$k=2$	$k=3$

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

$$X \overset{i.i.d}{\sim} Normal(0, 0.25)$$

(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)

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

(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:

γ	M	MSE $(E-est)$	MSE Percent Reduction(%) $(BMW$ vs. $E-est)$		
			$k=1$	$k=2$	$k=3$
where propensity score ***inappropriately*** specified (17) (18)					
		$X \overset{i.i.d}{\sim} Normal(0, 0.25)$			
(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 ***appropriately*** specified (15) (16)					
		$X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.5)$			
(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:

γ	$\sum_{j=1}^{8} \gamma_j$	M	MSE (NB Design)	MSE Percent Reduction(%) (BMW vs. NB Design)		
				$k=1$	$k=2$	$k=3$
$X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.5)$						
(1.0,1.0,1.0,1.0)	4	5	0.185	2.42	14.49	8.53
		10		9.62	15.79	11.68
		20		24.78	22.18	18.44
$X_1, X_2, X_3, X_4, X_5, X_6, X_7, X_8 \overset{i.i.d}{\sim} Bernoulli(0.5)$						
(1.0,1.0,1.0,1.0, 1.0,1.0,1.0,1.0)	8	5	0.222	-25.19	16.39	16.07
		10		-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;

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Application to Instinct Trial

- Cluster-level confounders:
  - Stroke Volume;
  - Population Density;
  - Percent male greater than 65;
  - Percent Female greater than 65;
- Matched-Pair Design: Optimally Matched on Stroke Volume and Population Density;
- BMW Design:
  - When $\gamma_j' s$ are unknown: $k = 2$; $M = 10$;

Application to Instinct Trial: BMW results

	Treatment Group					*Control Group*				
Strata	$ID(\widehat{\delta})$	X_1	X_2	X_3	X_4	$ID(\widehat{\delta})$	X_1	X_2	X_3	X_4
1	1 (0.33)	0.15	0.13	0	0	6 (0.35)	0.19	0.07	0	0
2	2 (0.38)	0.17	0.11	1	0	8 (0.35)	0.22	0.14	0	0
	11 (0.40)	0.22	0.14	1	0					
3	3 (0.63)	0.13	0.06	1	1	9 (0.63)	0.14	0.06	1	1
						19 (0.67)	0.25	0.15	1	1
4	4 (0.58)	0.12	0.06	0	1	12 (0.60)	0.07	0.06	1	1
5	14 (0.32)	0.13	0.07	0	0	13 (0.32)	0.13	0.09	0	0
	15 (0.31)	0.10	0.06	0	0					
6	17 (0.41)	0.24	0.12	1	0	10 (0.41)	0.26	0.18	1	0
	22 (0.43)	0.30	0.17	1	0					
7	20 (0.60)	0.08	0.06	1	1	16 (0.61)	0.10	0.07	1	1
						18 (0.61)	0.09	0.05	1	1
8	21 (0.60)	0.18	0.14	0	1	5 (0.61)	0.19	0.13	0	1
9	24 (0.62)	0.23	0.16	0	1	7 (0.62)	0.24	0.19	0	1
						23 (0.62)	0.11	0.07	1	1

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 $\binom{N}{\frac{N}{2}}$), e.g. $M = \infty$ and $k = 1$, the BMW design always lead to th 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.

Extension

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

Propensity Score

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

Propensity Score

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- Baseline category model to relates treatment to confounders:

$$\delta_{t,i} = Pr(Z = t \mid \mathbf{X}_i; \boldsymbol{\alpha}_t) = \exp\{\boldsymbol{\alpha}_t \mathbf{X}_i^T\} / \{1 + \exp\{\boldsymbol{\alpha}_1 \mathbf{X}_i^T\} + \exp\{\boldsymbol{\alpha}_2 \mathbf{X}_i^T\}\}$$

where $t = 1, 2, 3$ with $\boldsymbol{\alpha}_3 = 0$.

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

$$(\hat{\delta}_{1,i}, \hat{\delta}_{2,i}, \hat{\delta}_{3,i})$$

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- 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:

$$\delta\{(\eta_i^A, \eta_j^B)\} = \sqrt{(\hat{\delta}_{1,i}^A - \hat{\delta}_{1,j}^B)^2 + (\hat{\delta}_{2,i}^A - \hat{\delta}_{2,j}^B)^2 + (\hat{\delta}_{3,i}^A - \hat{\delta}_{3,j}^B)^2}$$

Optimal tripartite matching

How to optimally match on three groups?

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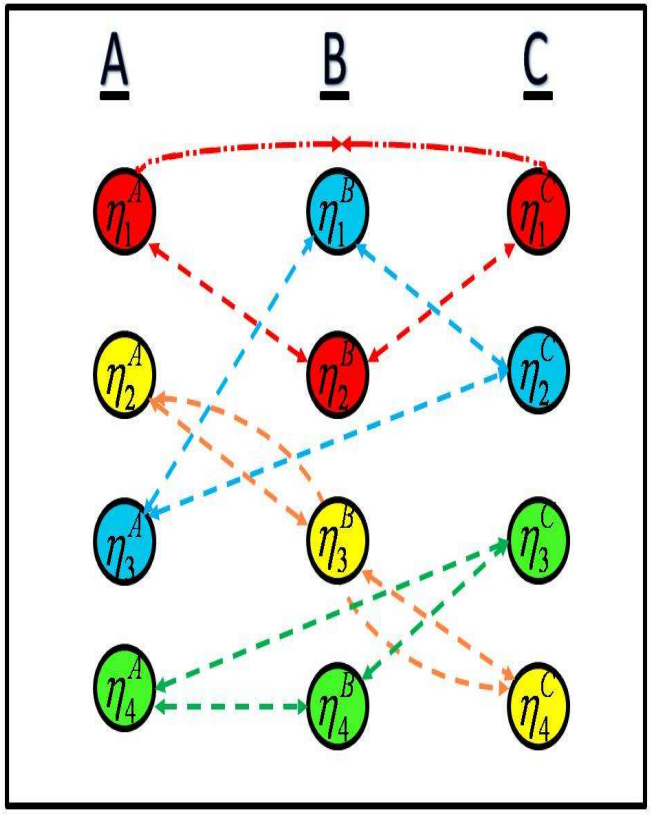

- Ad hoc approaches which may not lead to the optimal matching, but to the solutions that are close to optimal were developed.

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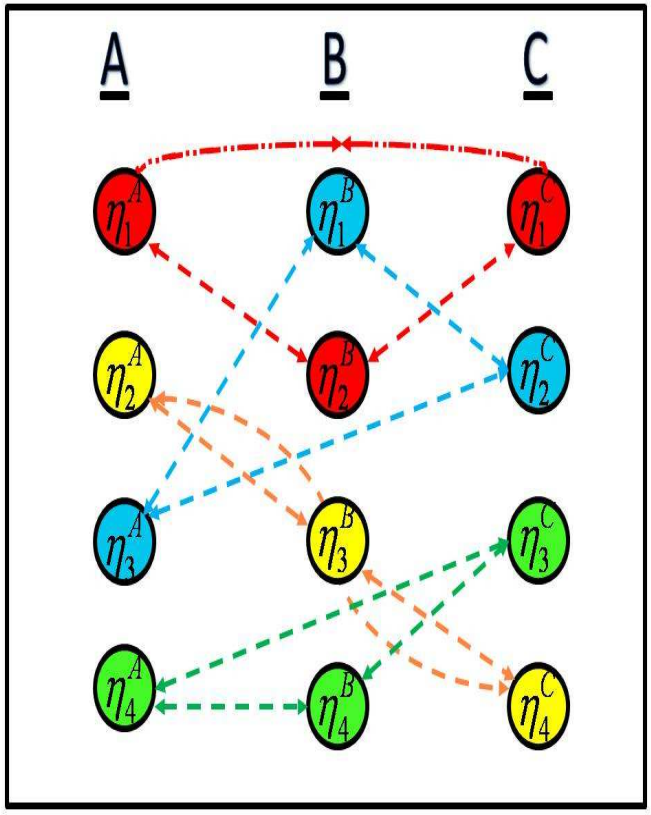

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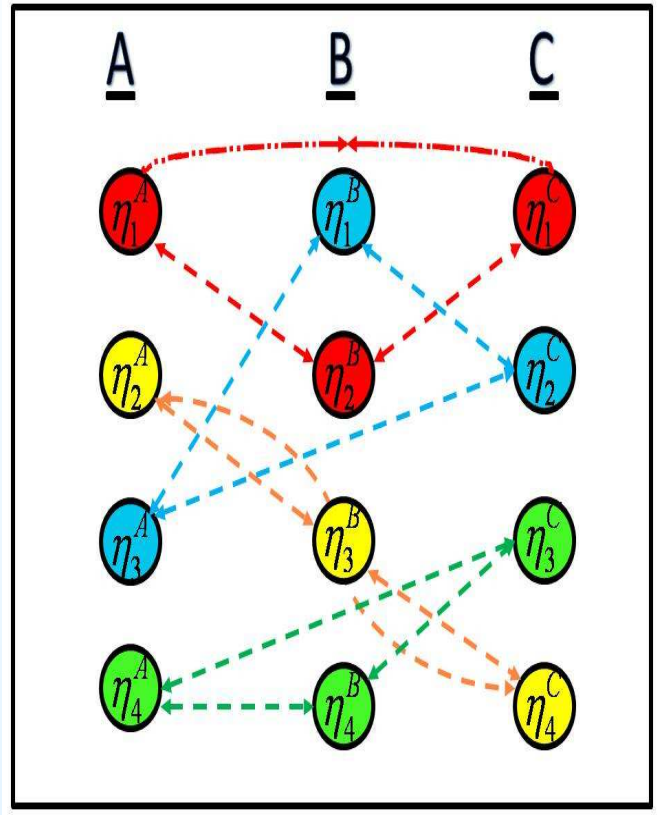

- The Optimal tripartite matching problem: NP complete problem;
- Given group Size m, number of comparisons = $(m!)^2$;
  - Group Size $m = 3$, number of comparisons = 36;
  - Group Size $m = 4$, number of comparisons = 576;
  - Group Size $m = 5$, number of comparisons = 14400;
  - Group Size $m = 6$, number of comparisons = 518400;
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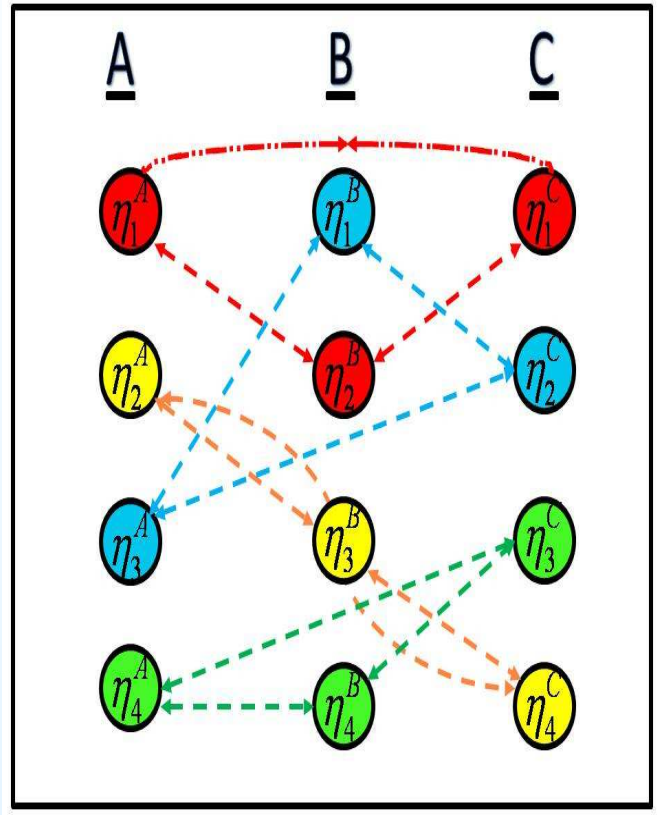

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Ad Hoc Method (I). Incomplete Block Design with Disjoint Pairs

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.

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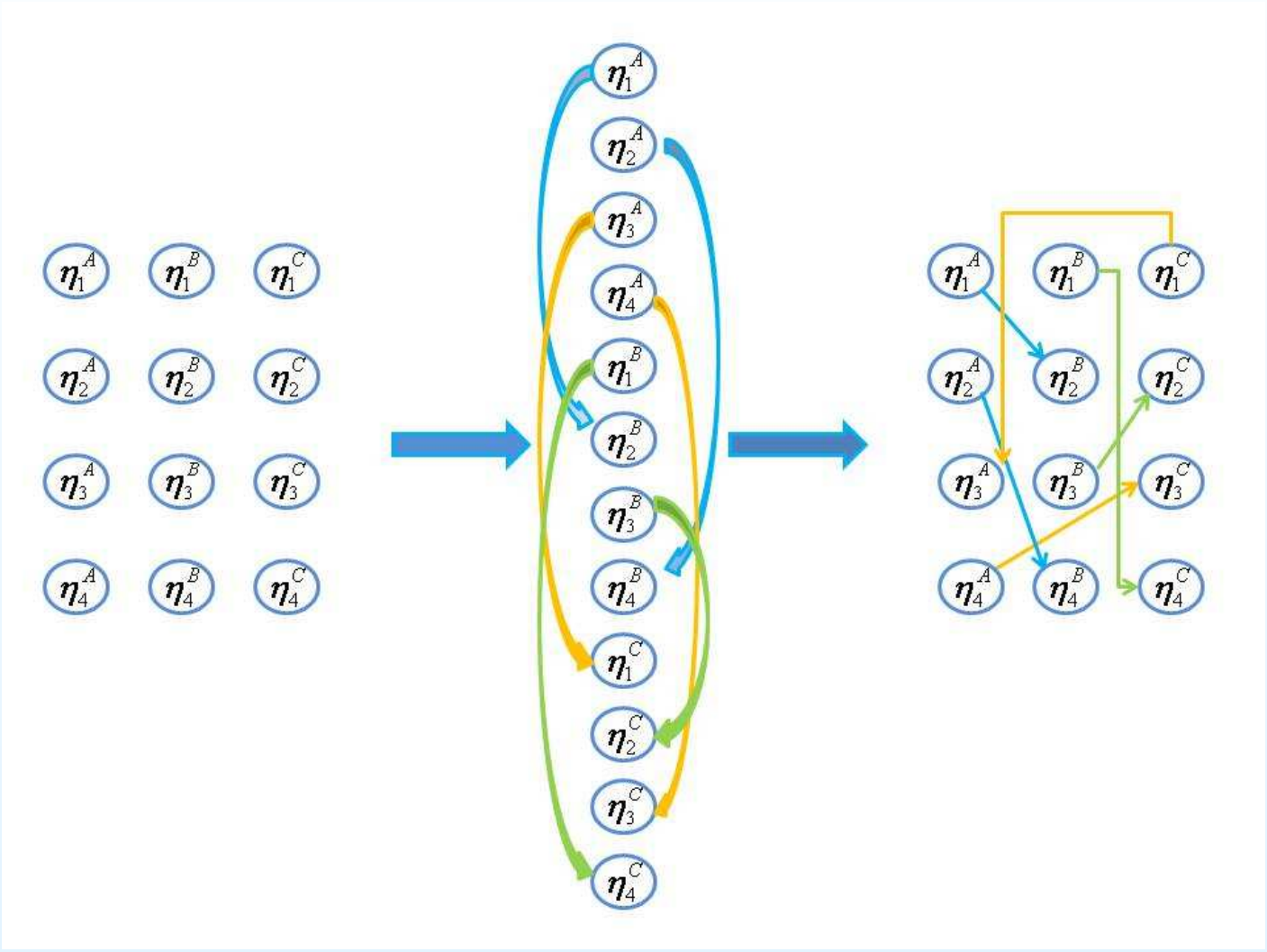
Bo and Rosenbaum (2004): P is an optimal non-bipartite matching with $\Delta(P) < +\infty$ if and only if P is also an optimal, feasible tripartite matching.

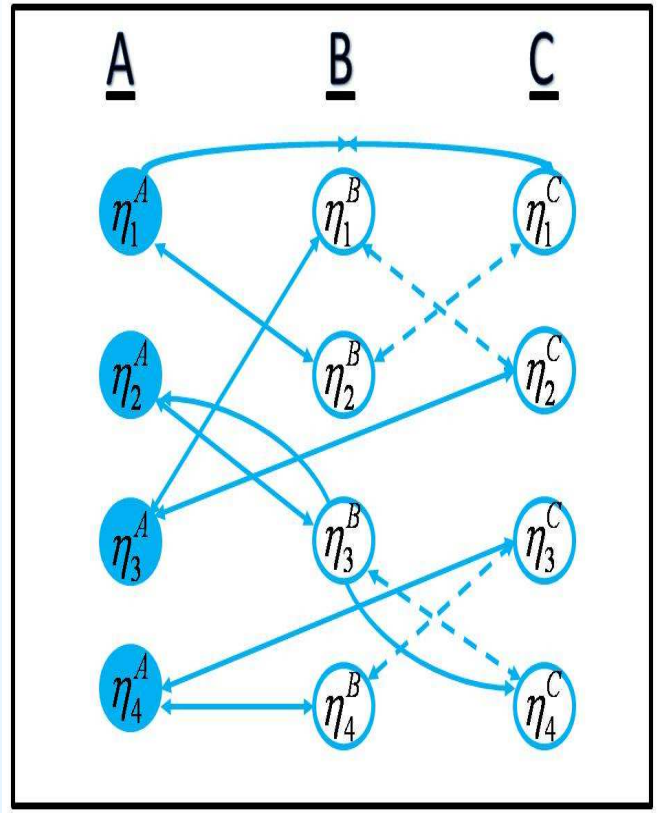
- Given a single set $\Theta = \mathcal{A} \bigcup \mathcal{B} \bigcup \mathcal{C} = (\eta_1^A, ..., \eta_{N/3}^A, \eta_1^B, ..., \eta_{N/3}^B, \eta_1^C, ...\eta_{N/3}^C)$;
- $$\delta\{(\eta_i^m, \eta_j^n)\} = \begin{cases} \sqrt{(\hat{\delta}_{1,i}^m - \hat{\delta}_{1,j}^n)^2 + (\hat{\delta}_{2,i}^m - \hat{\delta}_{2,j}^n)^2 + (\hat{\delta}_{3,i}^m - \hat{\delta}_{3,j}^n)^2} & \text{if } m \neq n; \\ +\infty & \text{if } m = n. \end{cases}$$
- 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



- $\Delta^*_{\mathcal{M}_\mathcal{A}} = \Delta^*_{\mathcal{M}_{\mathcal{A},\mathcal{C}}} + \Delta^*_{\mathcal{M}_{\mathcal{A},\mathcal{B}}} + \sum_{\omega\in\mathcal{M}^+_{\mathcal{B},\mathcal{C}}} \delta(\omega)$
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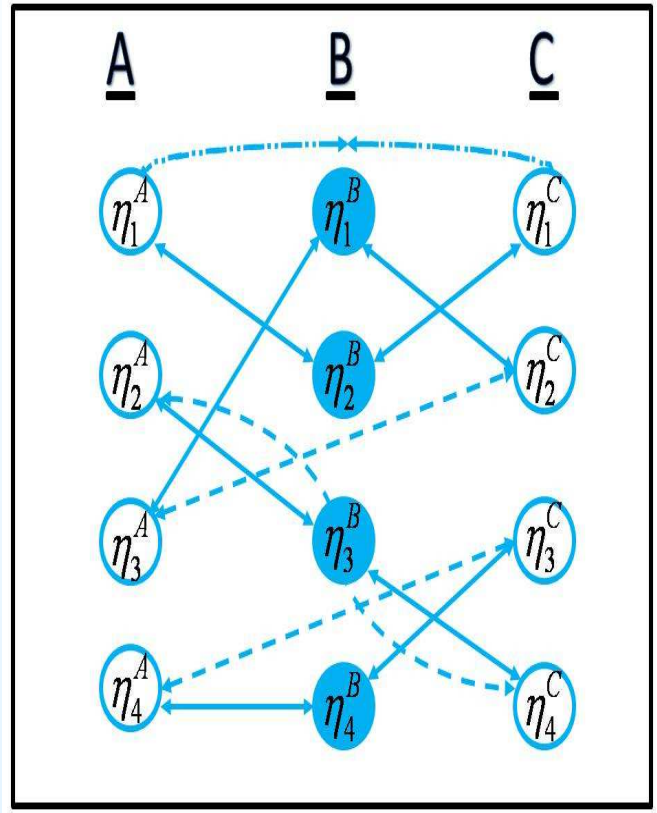

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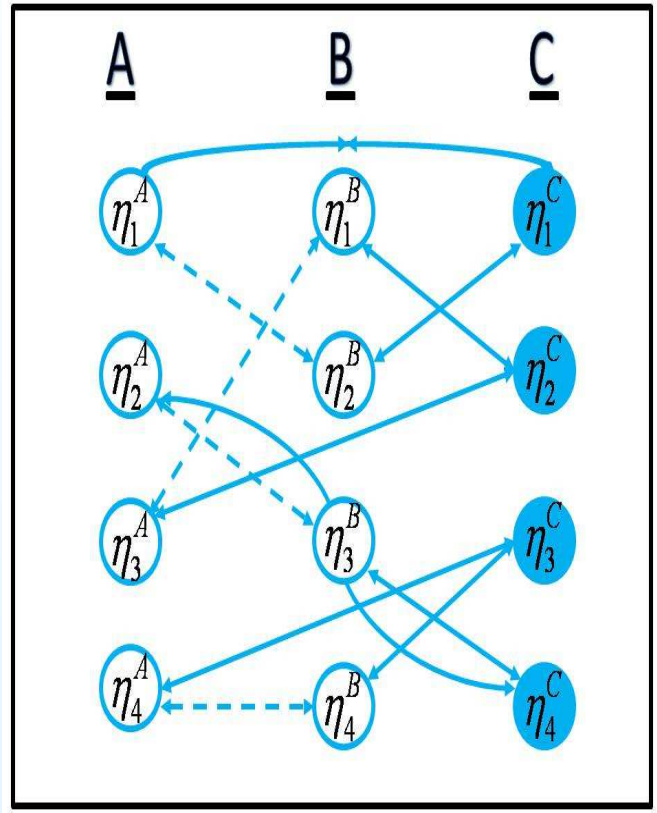

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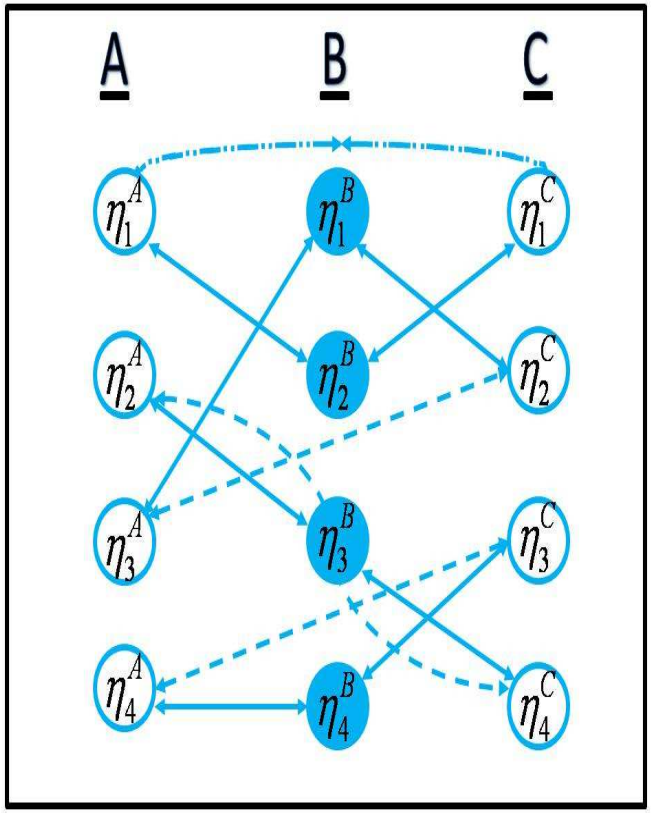
Ad Hoc Method (III). Asymmetric Tripartite Matching With Triples



- With group B as predefined reference group:
- $\Delta^*_{\mathcal{B}} = \Delta^*_{\mathcal{M}_{\mathcal{A},\mathcal{B}}} + \Delta^*_{\mathcal{M}_{\mathcal{B},\mathcal{C}}}$
- $\sum_{\omega \in \mathcal{M}^+_{\mathcal{A},\mathcal{C}}} \delta(\omega)$ is not taken into account;

The BMW Design with Three Arms: Assessment Model

Model: $Y_i = \alpha + \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma^T \mathbf{X}_i + \varepsilon_i$

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- Matched Samples (ATM and STM Design):

$$\widehat{\beta}_1^{ATM} = \widehat{\beta}_1^{STM} = \overline{y}_{\mathcal{A}} - \overline{y}_{\mathcal{C}}$$

$$MSE(\widehat{\beta}_1^{STM}) = \gamma^T \mathrm{Cov}^{**}(\overline{\mathbf{X}}_{\mathcal{A}} - \overline{\mathbf{X}}_{\mathcal{C}})\gamma + 6\sigma^2/N.$$

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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:
  $Y_i = \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma^T \mathbf{X}_i + \varepsilon_i, \quad i = 1, 2, ...N$
- true treatment effect: $\beta_1 = \beta_2 = 0.5$
- true confounding effects: $\gamma_j = \gamma,\ j = 1, ..., r$, where $\gamma\ = 0.5, 1.0, 1.5$
- covariate setting:
  - $X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim}$ Bernoulli(0.5) ;
  - $X_1, X_2 \overset{i.i.d}{\sim}$ Bernoulli(0.5) ; $X_3, X_4 \overset{i.i.d}{\sim} N(0, 0.25)$
- We consider sample sizes $N = 24$ or 36;

The BMW Design with Three Arms: Simulation Results $N = 24$

γ	M	MSE (CR)	MSE Percent Reduction(%) (ICB vs. CR Design)	(STM vs. CR Design)	(ATM vs. CR Design)	
			$\hat{\beta}_1 = \hat{\beta}_{AC}$	$\hat{\beta}_1 = \hat{\beta}_{AC}$	$\hat{\beta}_1$ or $\hat{\beta}_2$	$\hat{\beta}_{AB} = \hat{\beta}_1 - \hat{\beta}_2$
			$X_1, X_2, X_3, X_4 \overset{i.i.d}{\sim} Bernoulli(0.5)$			
0.5	100	0.312	-11.95	15.52	15.23	15.42
1.0	100	0.487	18.05	37.02	38.18	34.58
1.5	100	0.806	40.20	53.61	55.56	47.96
			$X_1, X_2 \overset{i.i.d}{\sim} Bernoulli(0.5); X_3, X_4 \overset{i.i.d}{\sim} N(0, 0.25)$			
0.5	100	0.288	-19.11	10.12	10.36	9.14
1.0	100	0.403	7.11	28.74	29.38	27.28
1.5	100	0.600	29.24	44.37	45.44	42.23

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- Model:

$$Y_i = \beta_1 I(Z_i = 1) + \beta_2 I(Z_i = 2) + \gamma X_i + \varepsilon_i, \quad i = 1, 2, ...18$$

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

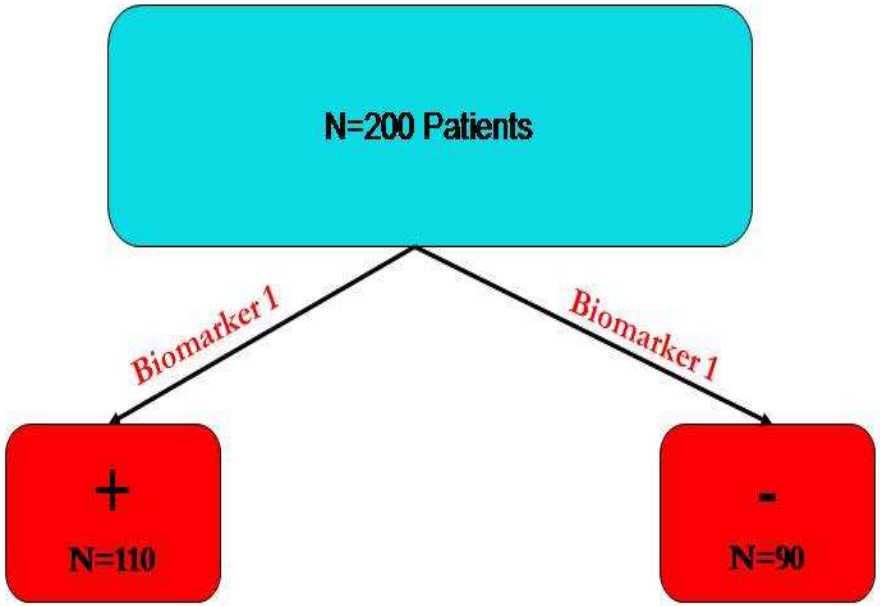
Discussion

- 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; $\surd$
  - The asymmetric quadripartite matching; $\surd$
  - Method of finding Optimal balanced incomplete block design through nonbipartite matching; $\times$
- 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 $\geq$ 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;

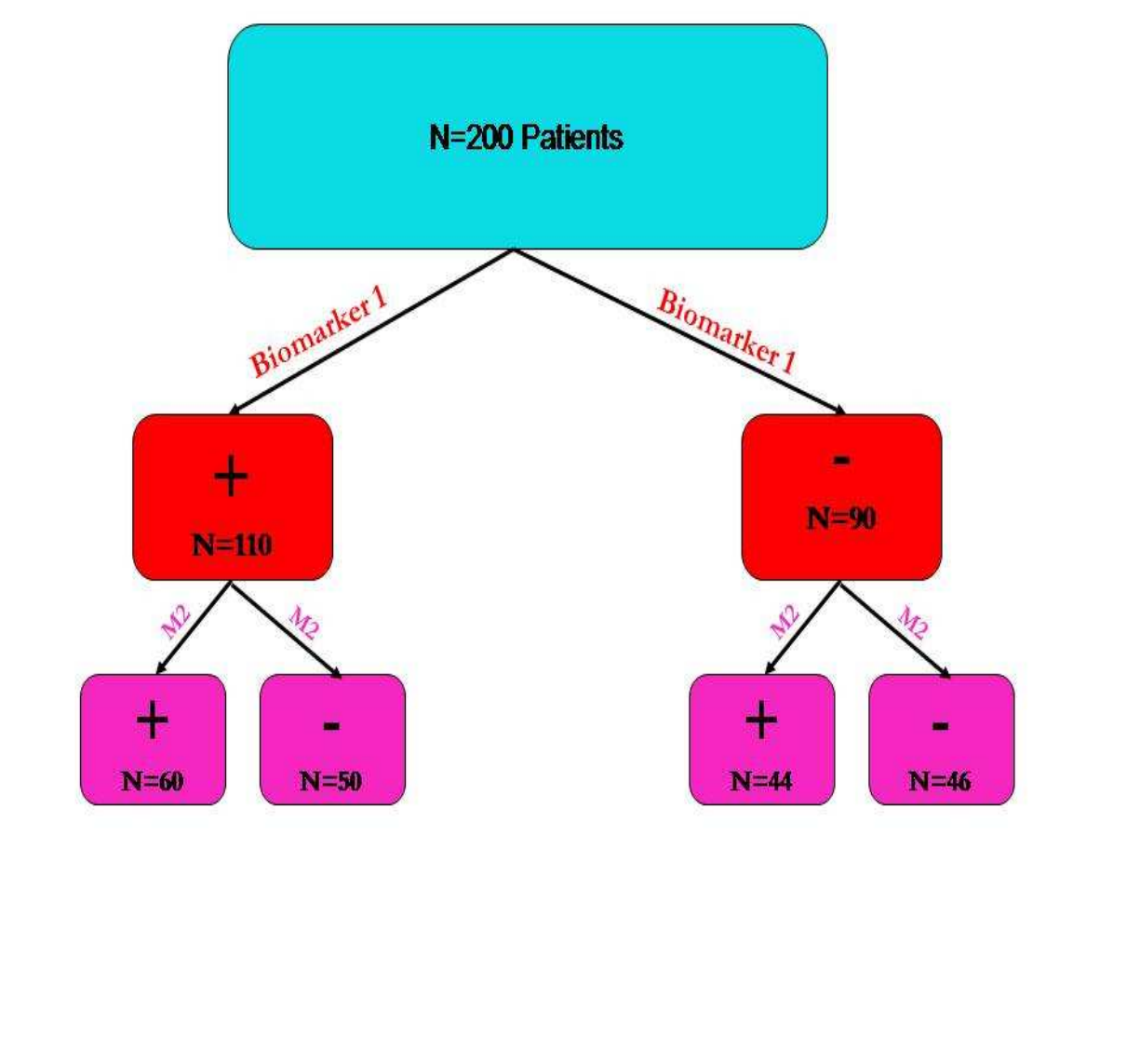
Future Work in Personalized Medicine

Personalized Medicine Trials Design: Biomarker-stratified Design

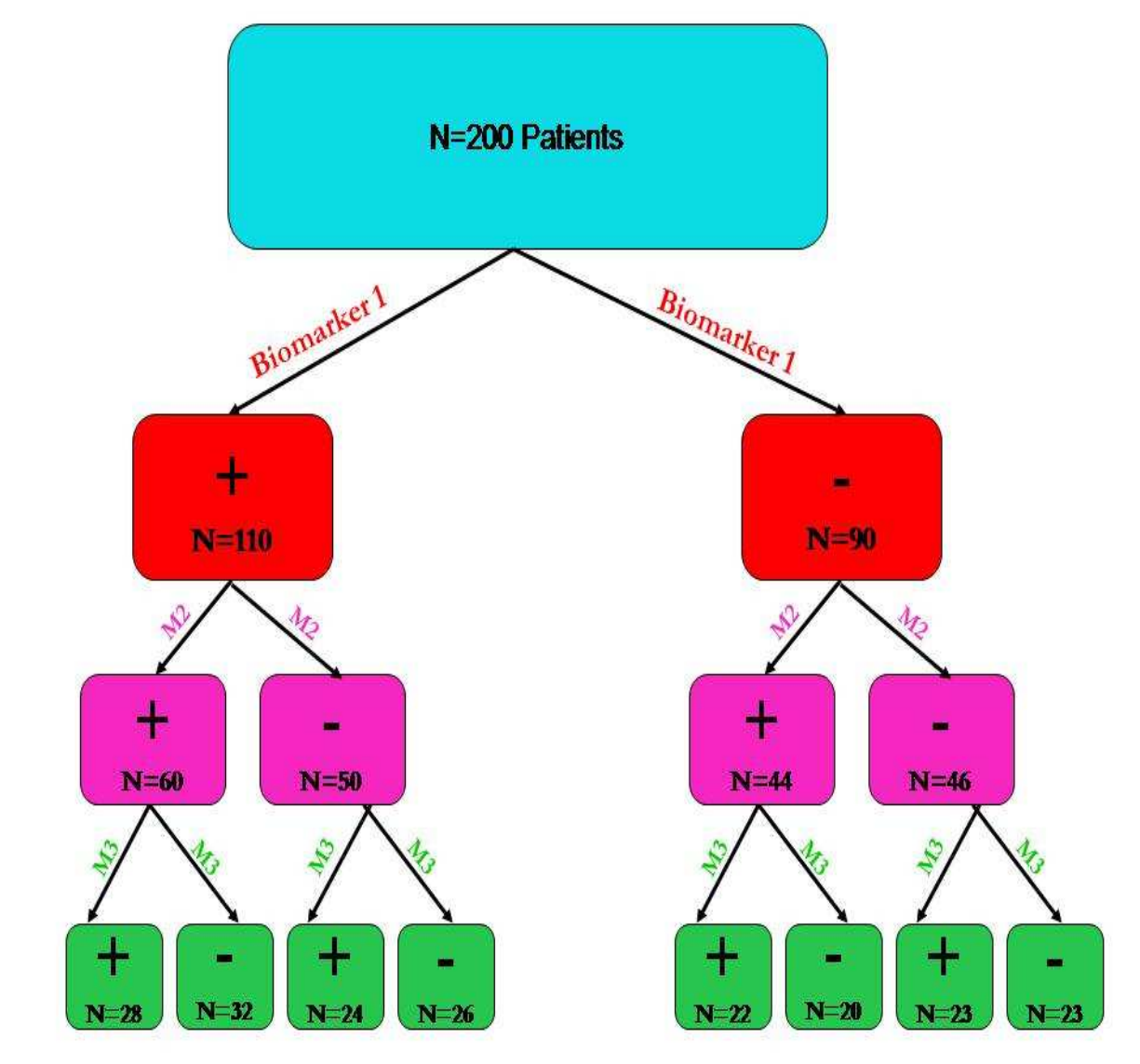
Personalized Medicine Trials Design: Biomarker-stratified Design



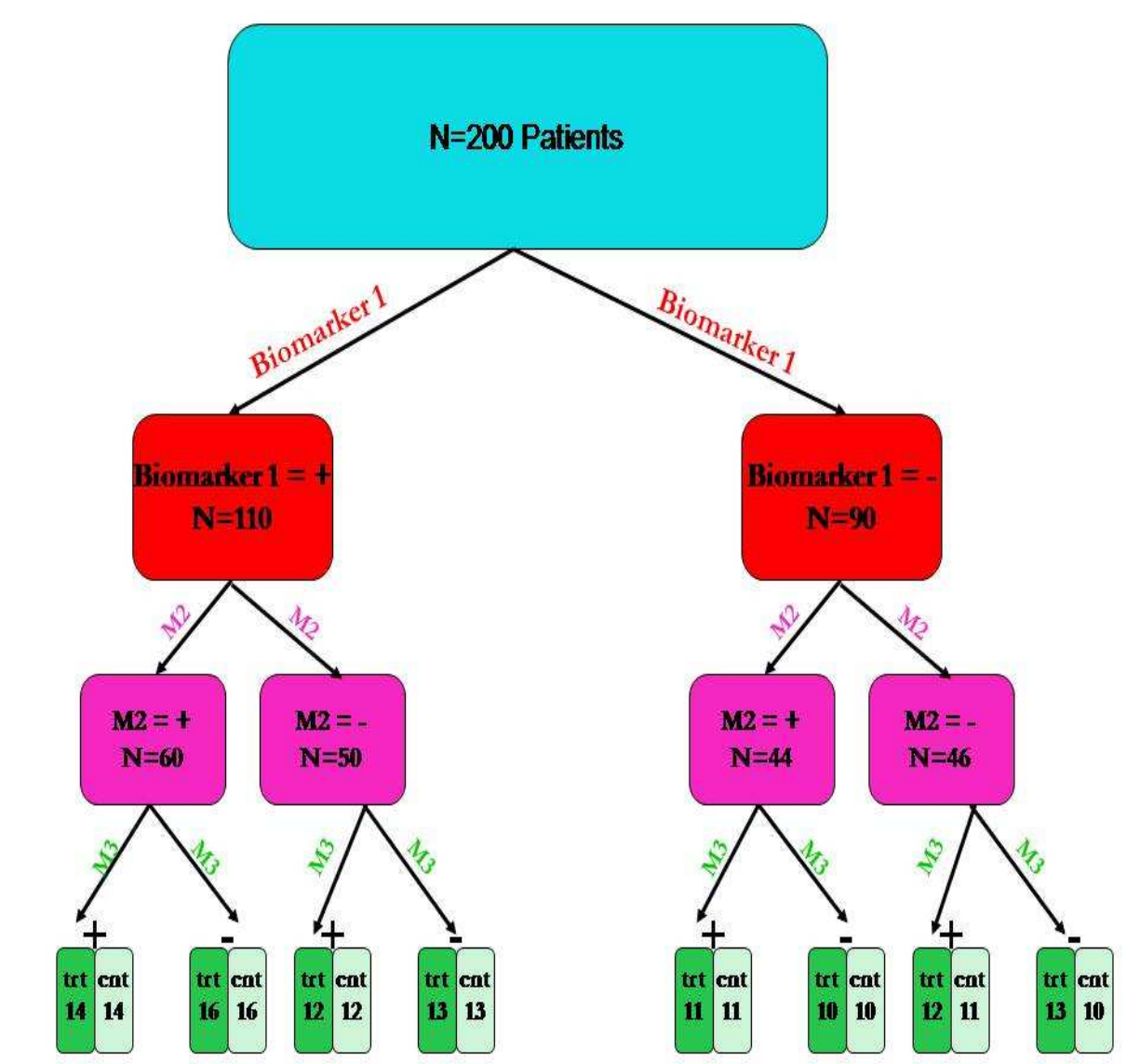
Personalized Medicine Trials Design: Biomarker-stratified Design



Personalized Medicine Trials Design: Biomarker-stratified Design



Personalized Medicine Trials Design: Biomarker-stratified Design



References

References

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