Randomization tests in the presence of selection bias

Diane Uschner and Ralf-Dieter Hilgers

Department for Medical Statistics, RWTH Aachen University

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Preliminaries

- Two-arm parallel group trial: groups E, C.
- Randomization sequence t_{obs} allocates N patients to E and C.

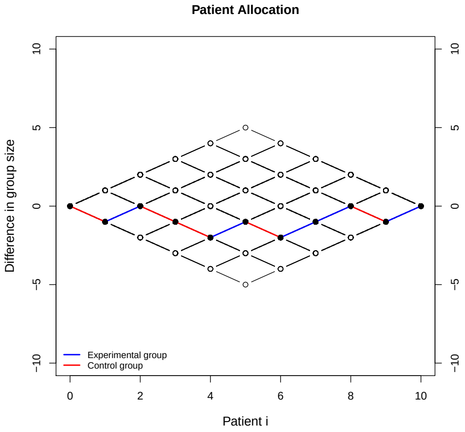

Figure: t_{obs} and reference set Ω

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Preliminaries

- Two-arm parallel group trial: groups E, C.
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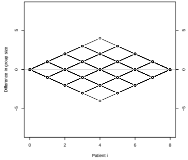
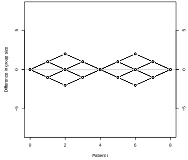
Definition

A *randomization procedure* $\mathcal{M}$ is a probability distribution on $\Gamma = \{E, C\}^N$. $\mathcal{M}$ *produces* the sequences

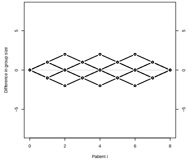
$$\Gamma_{\mathcal{M}} = \{t \in \Gamma \mid \mathbb{P}_{\mathcal{M}}(t) \neq 0\}$$



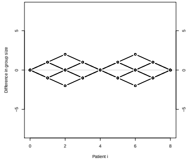
(a) Γ_{RAR}



(b) Γ_{PBR}



(c) Γ_{MP}



(d) Γ_{TBD}

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Rosenberger and Lachin (2016)

Randomization test

Null hypothesis

H_0: For each patient i the outcome y_i is the same disregarding of the treatment he receives.

1. Observe randomization sequence t_{obs}.
2. Observe the response $y_{obs} = (y_1, \dots, y_N)$.
   $\Rightarrow$ Treat the response as fixed!
3. Calculate the randomization distribution of the test statistic:

$$\forall t \in \Omega : \text{Compute} \quad S(t, y_{obs}).$$

4. Then the p-value is $p = \sum_{t \in \Omega} \mathbb{P}_{\mathcal{M}}(t) \cdot I(|S(t, y_{obs})| \geq |S(t_{obs}, y_{obs})|)$

Lehmann (1975)

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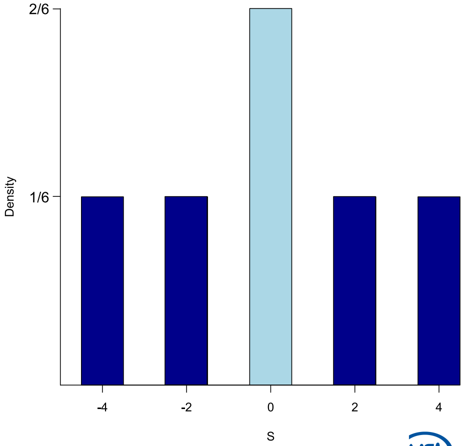
Example: Randomization test for RAR

Ranks of observed response: $y = (1, 2, 3, 4)$, test statistc $S_t = \sum_{i=1}^{4} y_i \cdot t_i - \sum_{i=1}^{4} y_i \cdot (1 - t_i)$

	t	$\mathbb{P}_{RAR}(t)$	S_t	$J_t = I(\lvert S_t \rvert \geq \lvert S_{obs} \rvert)$
1	E E C C	$1/6$	-4	1
*2	E C E C	$1/6$	-2	1
3	C E E C	$1/6$	0	0
4	E C C E	$1/6$	0	0
5	C E C E	$1/6$	2	1
6	C C E E	$1/6$	4	1

$$\Rightarrow p = \sum_t \mathbb{P}_{RAR}(t) \cdot J_t = 4/6$$



Two approach according to sample size

Exact Approach

Use the **complete set** $\Gamma_{\mathcal{M}}$ of sequences as the reference set Ω!

Monte Carlo Approach

Sample L sequences from $\Gamma_{\mathcal{M}}$ and use this sample as the reference set Ω!

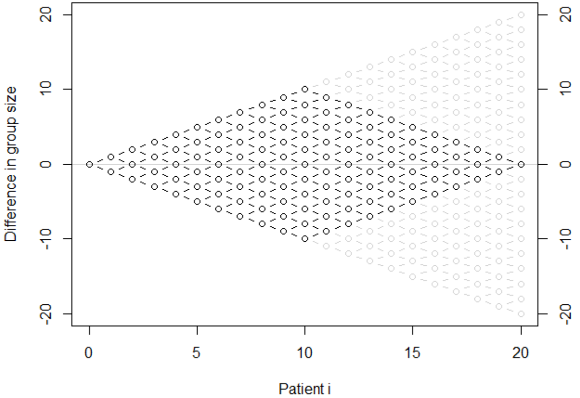


Figure: $|\Omega| = 184,756$

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Model for selection bias

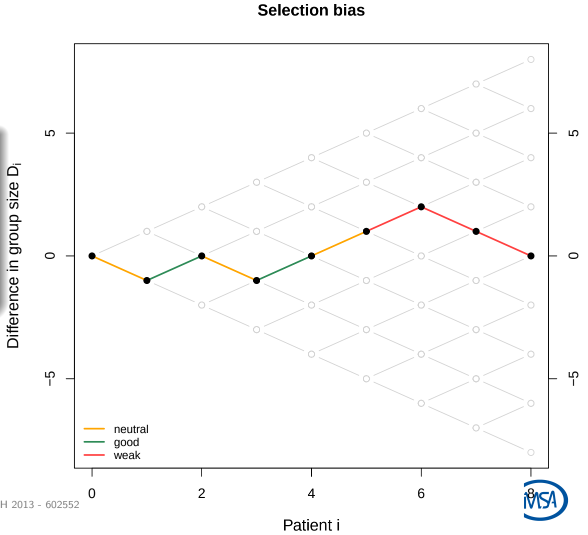
Assume now that the y_i are realizations of a random variable:

Convergence strategy

$$Y_i \sim \begin{cases} \mathcal{N}(\mu - \eta, \sigma^2) & D_{i-1} > 0 \\ \mathcal{N}(\mu, \sigma^2) & D_{i-1} = 0 \\ \mathcal{N}(\mu + \eta, \sigma^2) & D_{i-1} < 0 \end{cases}$$

Proschan (1994)
Blackwell and Hodges Jr. (1957)

$\rightarrow$ Investigator wants to assign patients with higher values to the experimental group.



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Settings

Let $T \in \Gamma \subset \{0,1\}^N$, D_i the imbalance after i patients and Y the random variable that models the response, overall group mean $\mu = 0$, d the detectable effect of the two-sided t-test for N patients, power 0.8 and level 0.05. We use the difference in ranks test statistic and investigate

- sample sizes $N = 12, 48$
- randomization procedures RAR, $PBR(4)$, $TBD(4)$ and $MP(2)$

for the settings:

Setting 1 - size

$Y_i \sim \mathcal{N}(-sgn(D_i) \cdot \eta, 1)$

1. $\eta = 0$
2. $\eta = d/4$
3. $\eta = d/2$

Setting 2 - power

$Y_i \sim \mathcal{N}(-sgn(D_i) \cdot \eta + d \cdot T_i, 1)$

1. $\eta = 0$
2. $\eta = d/4$
3. $\eta = d/2$

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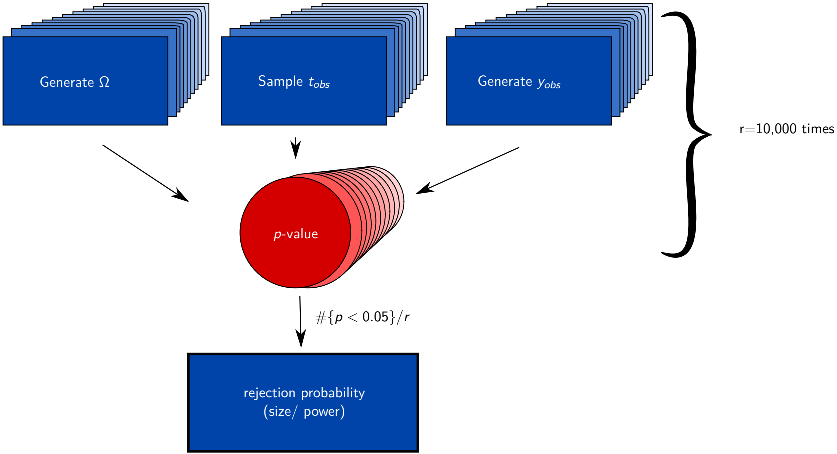
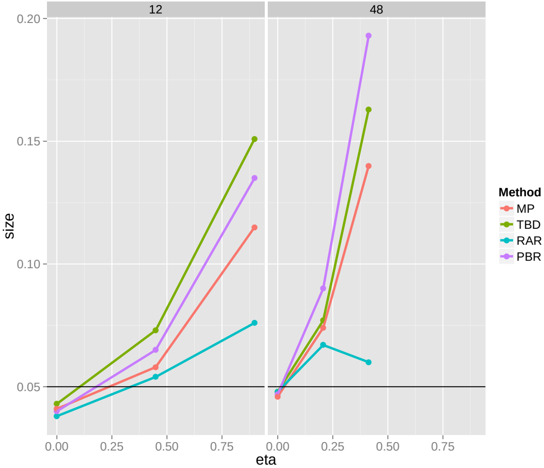
Simulations



Influence of selection bias on the test size



- For $N = 12$ and $d = 0$ all procedures yield a conservative randomization test.
- Larger sample size does not protect against selection bias.
- The type-I-error rate of the randomization test for RAR is least susceptible for selection bias.
- The type-I-error of MP, PBR and TBD is strongly elevated.

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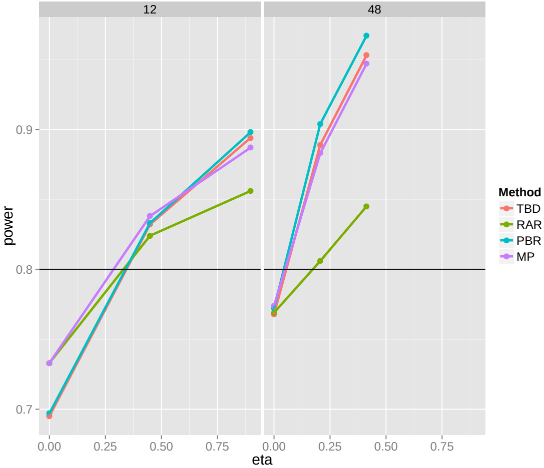
Influence of selection bias on the power



- For $d = 0$, the randomization test does not reach the nominal power.
- The power of MP, PBR and TBD is seriously elevated in case of selection bias.
- Random allocation rule is least affected by selection bias.
  $\Rightarrow$ Larger *reference set* less susceptible to selection bias.

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Conclusions

- Randomization tests generally provide valid basis for inference.
- The randomization test presented in this talk does not protect against selection bias.
- Aim: Develop a new randomization test (reference distribution + test statistic) that is not influenced by selection bias.

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References I

Blackwell, D. and J. L. Hodges Jr. (1957). Design for the control of selection bias. *Annals of Mathematical Statistics 25*, 449–460.

Lehmann (1975) Nonparametrics: Statistical Methods Based on Ranks

Proschan, M. (1994). Influence of selection bias on type 1 error rate under random permuted block designs *Statistica Sinica 4*, 219–231.

Rosenberger, W.F., and Lachin, J.M. (2016). Randomization in clinical trials - Theory and practice. Wiley.

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