

动态随机在RCT中的应用

Dynamic randomization in RCT

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随机化的几种方式 Randomization

简单随机
completely randomization
区组随机
randomized block design

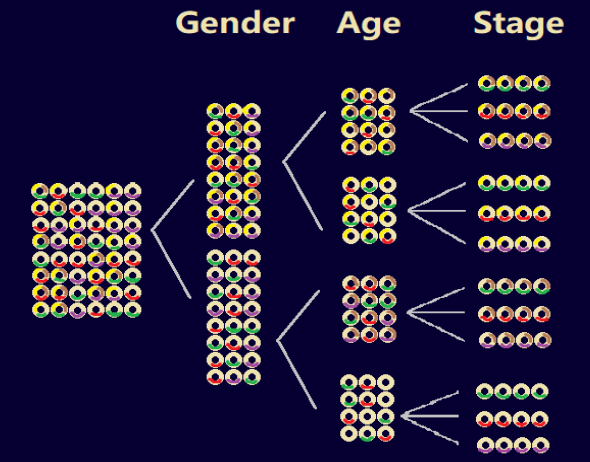
无法控制协变量
不能保证均衡



All depends on luck.

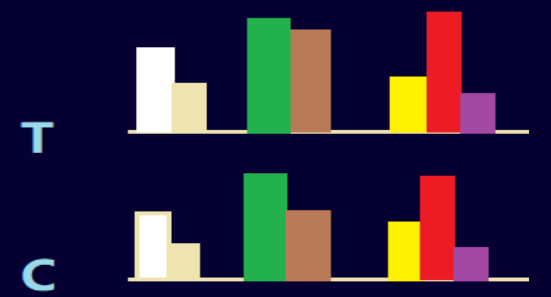
分层随机
stratified randomization

可均衡分层因素，
但会降低Power



动态随机
(最小化法 minimization)
Dynamic randomization

“白金标准^[1]”，
尤其适用于小样本
但操作较复杂



Ref. [1] Treasure T, Macrae KD. Minimisation: the platinum standard for trials? Randomisation doesn't guarantee similarity of groups; minimisation does. BMJ, 1998, 317: 362-363.

动态随机（最小化法）的原理 Principle of Dynamic Randomization

考虑需要控制的因素及水平，调整病例的入组，把病例以更高的概率分到能让组间均衡性更好的组里。保证组间基线资料综合的均衡性。

When a new patient enters the trial a set of marginal totals of previous randomizations is obtained by summing up all previous allocations in patients with the exact same profile. The method then attempts to balance these totals by allocating the treatment with the smallest value to the new patient. This minimizes the possible imbalance between subjects with a particular strata profile.

$$D_k = \sum_{i=1}^C \sum_{j=r_i}^J d_{ijk} w_i \quad \& \quad P_k$$

动态随机（最小化法）的步骤 Steps of Dynamic Randomization

- 1 确定哪些因素需要控制（协变量）
Select those factors(**covariates**) that should significantly affect the outcome.
- 2 确定各协变量的权重和分至目标组的概率
Weighting these variables(W_i). Set a random probability(P_k).
- 3 先用简单随机法入组1个或几个病例
Enroll one or several cases by completely randomization.
- 4 下一个病例入组之前先计算如果这个病例被分至试验组或对照组时，两组间的差异
The next one(**Case** n_{+1}), calculate the difference between groups if it assigned to the treat group(D_t) or the control group(D_c).
- 5 按照最小化原则，按照分配概率决定该病例的入组分配
If $D_t > D_c$, the Case n_{+1} more likely(With a P_k probability) to enter the control group, else, to the treat group

动态随机（最小化法）的效果

The Effect of Dynamic Minimization

Table 2
Comparisons of total imbalance scores B by allocation strategies

	Mean	0%	25%	50%	75%	100%
Panel (a): $n = 80$						
Minimization						
$P_k = 2/3$	0.155	0.008	0.080	0.130	0.204	0.747
$P_k = 3/4$	0.090	0.004	0.048	0.073	0.117	0.482
$P_k = 0.8$	0.067	0.004	0.035	0.056	0.084	0.380
$P_k = 0.9$	0.037	0.002	0.021	0.032	0.048	0.177
$P_k = 1$	0.024	0.003	0.015	0.021	0.031	0.084
Simple randomization	0.349	0.018	0.196	0.305	0.458	1.703
Panel (b): $n = 60$						
Minimization						
$P_k = 2/3$	0.249	0.016	0.129	0.213	0.331	1.073
$P_k = 3/4$	0.149	0.005	0.080	0.122	0.194	0.933
$P_k = 0.8$	0.119	0.004	0.062	0.098	0.153	0.539
$P_k = 0.9$	0.067	0.004	0.037	0.056	0.086	0.276
$P_k = 1$	0.044	0.003	0.026	0.040	0.055	0.275
Simple randomization	0.459	0.041	0.261	0.399	0.611	1.894

Table 4
Numbers of significant p -values comparing the base line covariates between treatment arms

Method	<u>Number of significant P-value < 0.05</u>		
	$n = 80$	$n = 60$	$n = 40$
Minimization			
$P_k = 2/3$	22	33	68
$P_k = 3/4$	2	6	16
$P_k = 0.8$	0	0	11
$P_k = 0.9$	0	0	2
$P_k = 1$	0	0	0
Simple randomization	248	225	262

动态随机的应用举例

For example

一项关于肿瘤患者预后的随机对照研究。认为性别、年龄、BMI、肿瘤分期、是否化疗是影响结局的因素，其权重分别为1、2、1、3、2。设定分配至目标组的概率为0.8。

The data of the first 7 patients are as follows:

weight	1	2	1	3	2	n
	Gender M/F	Age >45Yr/<=45Yr	BMI >28/<=28	Stage IV/III	Chemotherapy Y/N	
Control	3:1	3:1	3:1	2:2	2:2	4
Treat	1:3	1:2	2:1	2:1	3:0	3

还未入组的第8例患者为 男性、<45岁、BMI<28、IV期、有做化疗。

Which group should he enter?

动态随机的应用举例

For example

weight	1	2	1	3	2	n
	Gender (M/F)	Age (>45Yr/<=45Yr)	BMI (>28/<=28)	Stage (IV/III)	Chemotherapy (Y/N)	
Control	3:1	3:1	3:1	2:2	2:2	4
Treat	1:3	1:2	2:1	2:1	3:0	3

现在第8例患者男性、<45岁、BMI<28、IV期、有做化疗。
若该患者分到Control组，两组间差异为：

$$D_c = (4-1) \times 1 + (2-2) \times 2 + (2-1) \times 1 + (3-2) \times 3 + (3-3) \times 2 = 8$$

若该患者分到Treat组，两组间差异为：

$$D_t = (3-2) \times 1 + (3-1) \times 2 + (2-1) \times 1 + (3-2) \times 3 + (4-2) \times 2 = 13$$

因为 $D_c < D_t$,

所以第8例患者将以
更高的概率 (0.8) 分
到Control组

分享一个自己做的动态随机Excel工具

Share a little tool for dynamic randomization developed by myself

Probability		0.8					
Weights		1	2	1	3	2	
ID	group	Gender	>45yr	BMI>28	Stage	Chem	To which group
1	0	0	1	1	0	1	
2	1	1	1	1	1	1	
3	0	1	1	1	1	0	
4	1	0	0	0	0	1	
5	1	0	0	1	1	1	
6	0	1	0	0	1	1	
7	0	1	1	1	0	0	1
		1	0	0	1	1	

应用动态随机的注意事项 matters need attention

- 通常应设置一个小于1的概率(P_k), 而非100%按照 D_t 、 D_c 的大小来决定病例入组。

以引入随机元素, 减少选择偏倚。

Introducing a random element into minimization by only assigning the treatment chosen by minimization with a certain probability less than one. Pocock^[1]suggests that probabilities of 3/4 or 2/3 might be suitable choices.

- 协变量的权重设置要经过充分的专业讨论, 有足够的依据。

The weight setting must be fully discussed and have sufficient basis.

- 动态随机设计的研究, 是否能使用普通RCT的统计学检验方法, 学术界有一定争议, 但个人认为还是可以大胆使用的, 论文中可适当讨论。

The proportion (presumably high) of forced allocations that the method produces is still to be investigated. But anyway, Minimization is a standard randomization method^[2]

Ref.[1] Pocock S J. Clinical Trials: a Practical Approach[M]. Chichester: Wiley,1983: 84-87.

[2] Heritier S , Gebiski V , Pillai A . Dynamic balancing randomization in controlled clinical trials[J]. Statistics in Medicine, 2010, 24(24):3729-3741.

随机化的初心：均衡、避免偏倚
围绕这个宗旨可以探索更多新方法

