Optimal Crossover Designs for Comparing Test Treatments to a Control Treatment When Subject Effects are Random

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Outline

- A Taste of Optimal Designs
- Motivation from Statistics
  - Background
  - Results
- Construction of Optimal Designs
  - Characteristics of Optimal Designs
  - Guidelines for Construction
  - Methods of Constructions
- Further Problems

A design as a mapping

1	2	3	0	0	2	0	3	2	1
0	3	0	1	4	0	1	2	3	4
2	0	3	3	0	4	4	2	4	0

$d : (k, u) \mapsto i$ where $1 \leq k \leq p$, $1 \leq u \leq n$ and $0 \leq i \leq t$
In this example, $n = 10, p = 3, t = 4$.

What's special about these two designs?

0	0	0	2	3	1	2	3	1
1	2	3	0	0	0	1	2	3
2	3	1	1	2	3	0	0	0

1	3	2	3	2	0	1	3	0	2	1	0
2	1	3	2	0	3	3	0	1	1	0	2
0	0	0	1	1	1	2	2	2	3	3	3

Notations

- $n_{diu} = \sum_{k=1}^{p} I_{[d(k,u)=i]}$.
- $\tilde{n}_{diu} = \sum_{k=1}^{p-1} I_{[d(k,u)=i]}$.
- $l_{dik} = \sum_{u=1}^{n} I_{[d(k,u)=i]}$.
- $m_{dij} = \sum_{u=1}^{n} \sum_{k=1}^{p-1} I_{[d(k,u)=i,d(k+1,u)=j]}$.
- $r_{di} = \sum_{u=1}^{n} \sum_{k=1}^{p} I_{[d(k,u)=i]}$.
- $\tilde{r}_{di} = \sum_{u=1}^{n} \sum_{k=1}^{p-1} I_{[d(k,u)=i]}$.

In general, we need...

A design d is saided to be a totally balanced test-control incomplete crossover design (TBTCI) if:

1. Each element from $\{1, 2, ..., t\}$ show up in each column at most once.
2. Each element from $\{0, 1, ..., t\}$ is equally replicated in each row.
3. $|n_{d0u} - n_{d0v}| \leq 1$ and $|\tilde{n}_{d0u} - \tilde{n}_{d0v}| \leq 1$ for all $1 \leq u, v \leq n$.
4. m_{d0i}, m_{di0} and m_{dij} are constants across all $1 \leq i \neq j \leq t$ and $m_{dii} = 0$ for all $0 \leq i \leq t$.
5. r_{di} and $\tilde{r}_{di}$ are constants across all $1 \leq i \leq t$.
6. $\sum_{u=1}^{n} n_{d0u}n_{diu}, \sum_{u=1}^{n} n_{diu}n_{dju}, \sum_{u=1}^{n} \tilde{n}_{d0u}\tilde{n}_{diu}, \sum_{u=1}^{n} \tilde{n}_{diu}\tilde{n}_{dju}, \sum_{u=1}^{n} n_{d0u}\tilde{n}_{diu}, \sum_{u=1}^{n} \tilde{n}_{d0u}n_{diu}$, and $\sum_{u=1}^{n} n_{diu}\tilde{n}_{dju}$, are constants across all $1 \leq i \neq j \leq t$.

Let $N_d = (n_{diu})$ and $\tilde{N}_d = (\tilde{n}_{diu})$ when $0 \le i \le t$ and $1 \le u \le n$. Conditions 5 and 6 are equivalent to

$$N_d N_d' = \begin{pmatrix} a_1 & b_1 1_t' \\ b_1 1_t & (e_1 - f_1)I_t + f_1 J_t \end{pmatrix} \tag{1}$$

$$N_d \tilde{N}_d' = \begin{pmatrix} a_2 & b_2 1_t' \\ c_2 1_t & (e_2 - f_2)I_t + f_2 J_t \end{pmatrix} \tag{2}$$

$$\tilde{N}_d \tilde{N}_d' = \begin{pmatrix} a_3 & b_3 1_t' \\ b_3 1_t & (e_3 - f_3)I_t + f_3 J_t \end{pmatrix} \tag{3}$$

$$a_1 = \sum_{u=1}^n n_{d0u}^2 \quad b_1 = \sum_{u=1}^n n_{d0u} n_{d1u} \quad e_1 = \sum_{u=1}^n n_{d1u}^2 \quad f_1 = \sum_{u=1}^n n_{d1u} n_{d2u}$$

$$a_2 = \sum_{u=1}^n n_{d0u} \tilde{n}_{d0u} \quad b_2 = \sum_{u=1}^n n_{d0u} \tilde{n}_{d1u} \quad c_2 = \sum_{u=1}^n \tilde{n}_{d0u} n_{d1u} \quad e_2 = \sum_{u=1}^n n_{d1u} \tilde{n}_{d1u} \quad f_2 = \sum_{u=1}^n n_{d1u} \tilde{n}_{d2u}$$

$$a_3 = \sum_{u=1}^n \tilde{n}_{d0u}^2 \quad b_3 = \sum_{u=1}^n \tilde{n}_{d0u} \tilde{n}_{d1u} \quad e_3 = \sum_{u=1}^n \tilde{n}_{d1u}^2 \quad f_3 = \sum_{u=1}^n \tilde{n}_{d1u} \tilde{n}_{d2u}$$

Definition

A $p \times n$ array with symbols from $\{0, 1, 2, ..., t\}$ is said to be a crossover design if columns represent subjects, rows represent periods and symbols represent treatments.

- Our goal
  Compare the test treatments, $\{1, 2, ..., t\}$, with the control treatment $\{0\}$.
- Important notations
  - n: number of subjects/units/patients
  - p: number of periods
  - t: number of test treatments
  - r_{d0}: replications of the control treatment in design d.

An Example

	1	2	3	0	0	2	0	3	2	1
d:	0	3	0	1	4	0	1	2	3	4
	2	0	3	3	0	4	4	2	4	0

An Example

	1	2	3	0	0	2	0	3	2	1
d:	0	3	0	1	4	0	1	2	3	4
	2	0	3	3	0	4	4	2	4	0

$$n = 10, \quad p = 3, \quad t = 4 \quad r_{d0} = 9$$

An Example

$$
d: \begin{array}{cccccccccc}
1 & 2 & 3 & 0 & 0 & 2 & 0 & 3 & 2 & 1 \\
0 & 3 & 0 & 1 & 4 & 0 & 1 & 2 & 3 & 4 \\
2 & 0 & 3 & 3 & 0 & 4 & 4 & 2 & 4 & 0
\end{array}
$$

$$n = 10, \quad p = 3, \quad t = 4 \quad r_{d0} = 9$$

- n could be hundreds or thousands depending on the study.
- p is usually not large due to ethic or other issues.
- t is not large either; we will inverstigate $t + 1 \geq p \geq 3$.

An Example

$$
\begin{array}{cccccccccccc}
 & 1 & 2 & 3 & 0 & 0 & 2 & 0 & 3 & 2 & 1 \\
\text{d:} & 0 & 3 & 0 & 1 & 4 & 0 & 1 & 2 & 3 & 4 \\
 & 2 & 0 & 3 & 3 & 0 & 4 & 4 & 2 & 4 & 0
\end{array}
$$

$$n = 10, \quad p = 3, \quad t = 4 \quad r_{d0} = 9$$

- n could be hundreds or thousands depending on the study.
- p is usually not large due to ethic or other issues.
- t is not large either; we will investigate $t + 1 \geq p \geq 3$.
- \# of designs (identical up to an isomorphism): $\frac{(N+n-1)!}{t!n!(N-1)!} \geq \frac{1}{t!(N-1)!} n^{N-1}, N = (t+1)^p$.
- Isomorphism: in the sense of relabling the subjects and test treatments.

Model

$$Y_{dku} = \mu + \alpha_k + \beta_u + \tau_{d(k,u)} + \gamma_{d(k-1,u)} + \epsilon_{ku} \tag{4}$$
$$\beta_u \ iid\ N(0, \sigma_\beta^2), \quad \epsilon_{ku} \ iid\ N(0, \sigma^2), \quad \beta_u \perp\!\!\!\perp \epsilon_{ku}$$

- Y_{dku}: Response from unit (subject) u in period k in design d.
- α_k: Effect of period k.
- β_u: Effect of subject u.
- $d(k,u)$: Treatment specified by the design d for unit u in period k. (Control $\{0\}$; Test $\{1, 2, ...t\}$)
- τ_i: Direct effect of treatment i
- γ_i: Carryover effect of treatment i (by convention $\gamma_{d(0,u)} = 0$)

Model (In Matrix Form)

$$\begin{aligned} E(\mathbf{Y}_d) = & \quad 1_{np}\mu + P\boldsymbol{\alpha} + T_d\boldsymbol{\tau} + F_d\boldsymbol{\gamma} \\ var(\mathbf{Y}_d) = & \quad \sigma^2(I_n \otimes (I_p + \theta J_p)) \end{aligned} \tag{5}$$

Where

- $\theta = \sigma_\beta^2/\sigma^2$.
- $\boldsymbol{\alpha} = (\alpha_1, ..., \alpha_p)'$, $\boldsymbol{\tau} = (\tau_0, ...\tau_t)'$, $\boldsymbol{\gamma} = (\gamma_0, ..., \gamma_t)'$.
- $P = 1_n \otimes I_p$.
- T_d and F_d denote the treatment and carryover incidence matrices.
- $\otimes$ denote the Kronecker product.

The information matrix C_d for $\boldsymbol{\tau}$ is

$$C_d = T_d' V^{-1/2} pr^{\perp} (V^{-1/2}[1_{np}|P|F_d]) V^{-1/2} T_d \tag{6}$$

where $V = I_n \otimes (I_p + \theta J_p)$ which depends on θ only,
and $pr^{\perp} A = I - A(A'A)^{-} A'$ is a projection.

- If $\theta = \infty$ (Hedayat and Yang (2005))
  C_d becomes the information matrix for the model with fixed subject effects (β_u is nonrandom.)
- If $\theta = 0$
  C_d becomes the information matrix for the model without subject effects ($\beta_u \equiv 0$)

The information matrix for $(\tau_1 - \tau_0, \tau_2 - \tau_0, ..., \tau_t - \tau_0)'$ is

$$M_d = T' C_d T \quad where \quad T = \begin{pmatrix} 0_{1\times t} \\ I_{t\times t} \end{pmatrix} \tag{7}$$

Thus, M_d can be simply obtained from C_d by deleting the first row and the first column of C_d.

- A-Optimal: $\min_d \sum_{i=1}^t Var(\widehat{\tau_i - \tau_0})$ (i.e. $\min_d Tr(M_d^{-1})$)

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- A-Optimal: $\min_d \sum_{i=1}^t Var(\widehat{\tau_i-\tau_0})$ (i.e. $\min_d Tr(M_d^{-1})$)
- MV-Optimal: $\min_d \max_{1\le i\le t} Var(\widehat{\tau_i-\tau_0})$

Lemma

An A-optimal design is also an MV-optimal design if its information matrix, M_d, is a completely symmetric matrix.

How to find $d^* = argmin_d Tr(M_d^{-1})$

$Tr(M_d^{-1}) \geq B_1(d) \geq B_2(d) \geq B_3(d) ... \geq B_m(d) \geq B_0$

1. $B_i, i \geq 1$ are functions of d; B_0 is a constant depending on n, p, t, θ.
2. Each inequality should hold for every competing design d.
3. There should exist a design d^* with all the equalities hold, i.e. $Tr(M_{d^*}^{-1}) = B_0$

Then we have $Tr(M_d^{-1}) \geq Tr(M_{d^*}^{-1})$.

Note that $Tr(M_d^{-1})$ is essentially a complicated function of the variables n_{diu}, $\tilde{n}_{diu}$, l_{dik}, m_{dij}, r_{di} and $\tilde{r}_{di}$ for $0 \leq i \neq j \leq t$ and $1 \leq k \leq p$.

The first step:

$$\begin{aligned}
C_d =& T_d' V^{-1/2} pr^{\perp}(V^{-1/2}[1_{np}|P|F_d]) V^{-1/2} T_d \\
\leq& T_d' V^{-1/2} pr^{\perp}(1_{np}|V^{-1/2} F_d) V^{-1/2} T_d \qquad (8) \\
=& T_d' V^{-1/2} pr^{\perp}(1_{np}) V^{-1/2} T_d \qquad (9) \\
&- T_d' V^{-1/2} pr^{\perp}(1_{np}) V^{-1/2} F_d \\
&\times (F_d' V^{-1/2} pr^{\perp}(1_{np}) V^{-1/2} F_d)^{-} \\
&\times F_d' V^{-1/2} pr^{\perp}(1_{np}) V^{-1/2} T_d
\end{aligned}$$

In (8), $A \leq B$ means $B - A$ is n.n.d. and the equality holds when $l_{dik} = r_{di}/p, i = 0, 1, ..., t$
Note that the matrix under the operator $pr^{\perp}$ becomes easy to evaluate.
The equality (9) uses the following fact:
$pr^{\perp}([A|B]) = pr^{\perp}(A) - pr^{\perp}(A)B(B'pr^{\perp}(A)B)B'pr^{\perp}(A)$

A middle step: $Tr(M_d^{-1}) \geq \frac{t(t-1)^2}{x_0} + \frac{t}{y_0}$ where $x_0 = \alpha - \frac{\beta^2}{\gamma}$ with

$$\alpha = \frac{1+\theta p - \theta}{1+\theta p}(tnp - tr_{d0}) - \frac{t\sum_{i=1}^{t} r_{di}^2 - r_{d0}^2}{(1+\theta p)pn} - r_{d0} + \frac{\theta \sum_{u=1}^{n} n_{d0u}^2}{1+\theta p}$$

$$\beta = t\sum_{i=1}^{t} m_{dii} + \frac{r_{d0}}{p} - l_{d01} - m_{d00} - \frac{\theta t}{1+\theta p}\sum_{i=1}^{t}\sum_{u=1}^{n} n_{diu}\tilde{n}_{diu}$$

$$- \frac{t}{(1+\theta p)pn}\sum_{i=1}^{t} r_{di}\tilde{r}_{di} + \frac{\theta}{1+\theta p}\sum_{u=1}^{n} n_{d0u}\tilde{n}_{d0u} + \frac{r_{d0}\tilde{r}_{d0}}{(1+\theta p)pn}$$

$$\gamma = (t+1-\frac{2}{p} - \frac{\theta t}{1+\theta p})(n(p-1) - \tilde{r}_{d0}) - \frac{n}{p}(p-1)^2 - \frac{t}{(1+\theta p)pn}\sum_{i=1}^{t} \tilde{r}_{di}^2$$

$$+ \frac{\tilde{r}_{d0}^2}{(1+\theta p)pn} + \frac{\theta}{1+\theta p}\sum_{u=1}^{n} \tilde{n}_{d0u}^2$$

and

$$y_0 = \left(r_{d0} - \frac{\theta}{1+\theta p} \sum_{u=1}^{n} n_{d0u}^2 - \frac{r_{d0}^2}{(1+\theta p)pn} \right)$$
$$- \left\{ (n(p-1) - \tilde{r}_{d0}) \left(m_{d00} - \frac{\theta}{1+\theta p} \sum_{u=1}^{n} n_{d0u}\tilde{n}_{d0u} - \frac{1}{(1+\theta p)pn} r_{d0}\tilde{r}_{d0} \right)^2 \right.$$
$$\left. + \tilde{r}_{d0} \left(\frac{r_{d0}}{p} - l_{d01} - m_{d00} + \frac{\theta}{1+\theta p} \sum_{u=1}^{n} n_{d0u}\tilde{n}_{d0u} + \frac{1}{(1+\theta p)pn} r_{d0}\tilde{r}_{d0} \right)^2 \right\}$$
$$\times \left\{ n(p-1) \left(\tilde{r}_{d0} - \frac{\theta}{1+\theta p} \sum_{u=1}^{n} \tilde{n}_{d0u}^2 - \frac{\tilde{r}_{d0}^2}{(1+\theta p)pn} \right) - \frac{\tilde{r}_{d0}^2}{p} \right\}^{-1}.$$

- $\Omega_{n,p,t}$: The collection of all the designs with the number of subjects n, number of periods p, number of test treatments t.
- $\Lambda_{n,p,t}$: A subclass of $\Omega_{n,p,t}$ with the restrictions that the control treatment is equally replicated in each period and no treatment is immediately preceded by itself. ($l_{d0k} = r_{d0}/p$ and $m_{dii} = 0$ for all $1 \leq k \leq p$ and $0 \leq i \leq t$)

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Lemma

When $t \geq 3$ and $t + 1 \geq p \geq 3$, $Tr(M_d^{-1}) \geq B_m(d) = f(n, p, t, r_{d0}, \theta)$ for all designs in $\Lambda_{n,p,t}$. The equality is obtained by a design in a form of TBTCI. When $p = 3, t = 2$, the conclusion still holds but only within a subclass of $\Lambda_{n,p,t}$ in which $r_{d0}/n \geq 0.6306$.

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There is no closed form for $argmin_r f(n,p,t,r,\theta)$.
$f(n,p,t,r_{d0},\theta) = t(t-1)^2/\tilde{x}_0 + t/\tilde{y}_0$ where $\tilde{x}_0$ and $\tilde{y}_0$ are derived from x_0 and y_0 by replacing all of the variables therein related to d with functions of r_{d0}.

Theorem

When $t \geq 3$ and $t+1 \geq p \geq 3$, a design d^* is optimal among designs in $\Lambda_{n,p,t}$ if it is a TBTCI and r_{d^*0} minimizes $f(n,p,t,r_{d0},\theta)$ given n,p,t,θ. When $p=3, t=2$, the design d^* is optimal in the same sense as in the lemma.

Remark: Similar results can be found in Hedayat and Yang (2005) when $\theta = \infty$. We extend the result for any value of $\theta \geq 0$.

Examples of TBTCI designs

- $TBTCI(9, 3, 3, 9)$

0	0	0	2	3	1	2	3	1
1	2	3	0	0	0	1	2	3
2	3	1	1	2	3	0	0	0

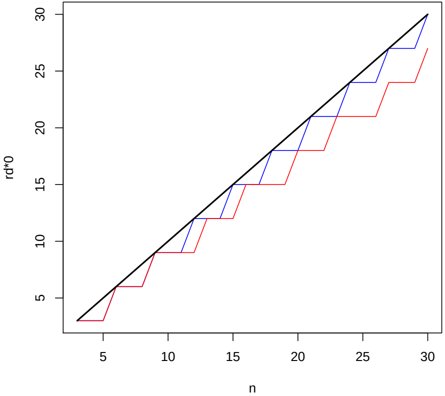
- $TBTCI(12, 3, 3, 9)$

1	3	2	3	2	0	1	3	0	2	1	0
2	1	3	2	0	3	3	0	1	1	0	2
0	0	0	1	1	1	2	2	2	3	3	3

Remark: $TBTCI(n, p, t, r_{d0})$ denotes a TBTCI with n units, p periods, t test treatments and r_{d0} replications of the control treatment.

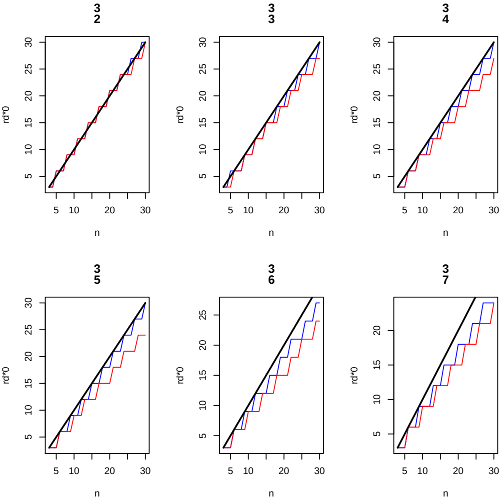
Graphical Description: $p = 3$ and $t = 4$

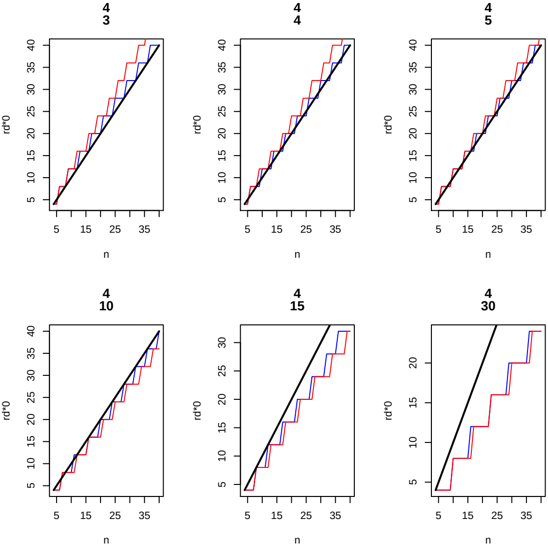
The optimal r_{d^*0} as a function of n in the sense of minimizing $f(n, p, t, r_{d0}, \theta)$.



- $\theta \geq 0$ is unkown but predetermined.
- The curves correspond to $\theta = \infty$ and $\theta = 0$.
- The bold line represents the equation $r_{d^*0} = n$.
- Whenever the curve for θ crosses the bold line, we have $r_{d^*0} = n$.
- r_{d^*0} is slightly smaller than n in general.
- r_{d^*0} jumps by $p = 3$ each time for any value of θ.

p=3 and t=2,3,...,7




4
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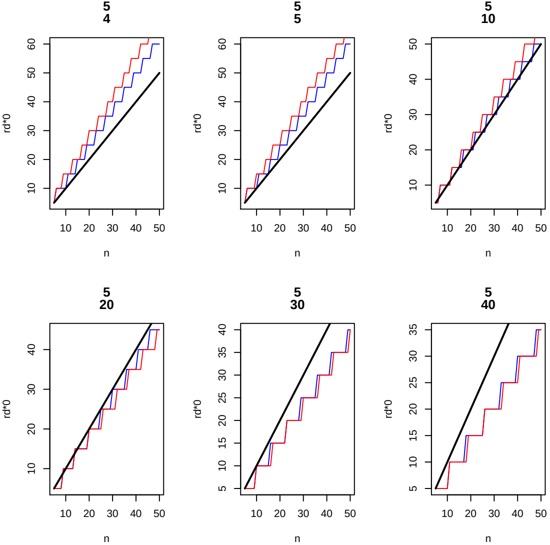
5 10 15 20 25 30 35 40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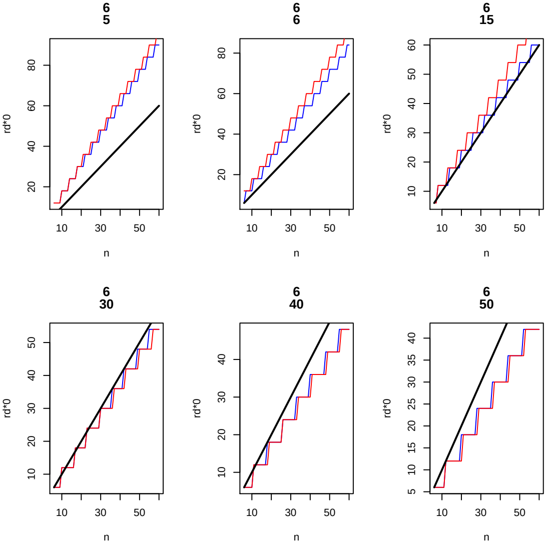
rd*0
n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6
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6
30
6
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6
50
rd*0
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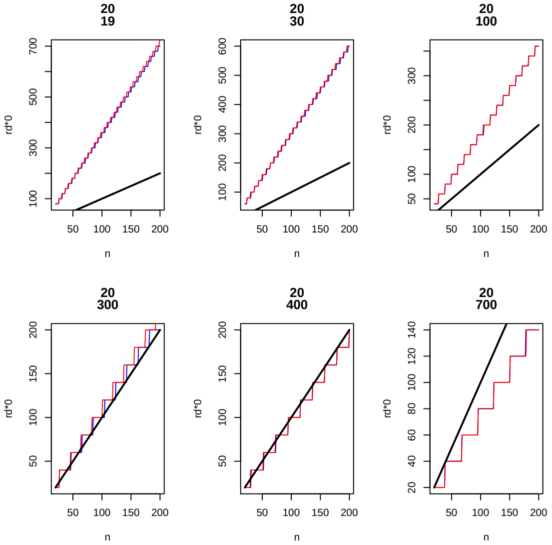
10
30
50


20
19
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30
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100
20
300
20
400
20
700
rd*0
n

Revisit the Notations

- $n_{diu} = \sum_{k=1}^{p} I_{[d(k,u)=i]}$.
- $\tilde{n}_{diu} = \sum_{k=1}^{p-1} I_{[d(k,u)=i]}$.
- $l_{dik} = \sum_{u=1}^{n} I_{[d(k,u)=i]}$.
- $m_{dij} = \sum_{u=1}^{n} \sum_{k=1}^{p-1} I_{[d(k,u)=i,d(k+1,u)=j]}$.
- $r_{di} = \sum_{u=1}^{n} \sum_{k=1}^{p} I_{[d(k,u)=i]}$.
- $\tilde{r}_{di} = \sum_{u=1}^{n} \sum_{k=1}^{p-1} I_{[d(k,u)=i]}$.

Revisit the Definition

A design d is saided to be a totally balanced test-control incomplete crossover design (TBTCI) if:

1. Each element from $\{1, 2, ..., t\}$ show up in each column at most once.
2. Each element from $\{0, 1, ..., t\}$ is equally replicated in each row.
3. $|n_{d0u} - n_{d0v}| \leq 1$ and $|\tilde{n}_{d0u} - \tilde{n}_{d0v}| \leq 1$ for all $1 \leq u, v \leq n$.
4. m_{d0i}, m_{di0} and m_{dij} are constants across all $1 \leq i \neq j \leq t$ and $m_{dii} = 0$ for all $0 \leq i \leq t$.
5. r_{di} and $\tilde{r}_{di}$ are constants across all $1 \leq i \leq t$.
6. $\sum_{u=1}^{n} n_{d0u}n_{diu}, \sum_{u=1}^{n} n_{diu}n_{dju}, \sum_{u=1}^{n} \tilde{n}_{d0u}\tilde{n}_{diu}, \sum_{u=1}^{n} \tilde{n}_{diu}\tilde{n}_{dju}, \sum_{u=1}^{n} n_{d0u}\tilde{n}_{diu}, \sum_{u=1}^{n} \tilde{n}_{d0u}n_{diu}$, and $\sum_{u=1}^{n} n_{diu}\tilde{n}_{dju}$, are constants across all $1 \leq i \neq j \leq t$.

Revisit (Continued)

Let $N_d = (n_{diu})$ and $\tilde{N}_d = (\tilde{n}_{diu})$ with the dimension of $0 \le i \le t$ and $1 \le u \le n$. Conditions 5 and 6 are equivalent to

$$N_d N_d' = \begin{pmatrix} a_1 & b_1 1_t' \\ b_1 1_t & (d_1 - e_1) I_t + e_1 J_t \end{pmatrix} \tag{10}$$

$$N_d \tilde{N}_d' = \begin{pmatrix} a_2 & b_2 1_t' \\ c_2 1_t & (d_2 - e_2) I_t + e_2 J_t \end{pmatrix} \tag{11}$$

$$\tilde{N}_d \tilde{N}_d' = \begin{pmatrix} a_3 & b_3 1_t' \\ b_3 1_t & (d_3 - e_3) I_t + e_3 J_t \end{pmatrix} \tag{12}$$

For $r_{d0} < n, p = 3$

Definition

A type I orthogonal array $OA_I(n, k, s, t)$ is a $k \times n$ array based on s symbols, where the columns of any $t \times n$ subarray contains all $s!/(s-t)!$ permutations of t distinct symbols.

Theorem

A type I orthogonal array $OA_I(t(t+1), 3, t+1, 2)$ *and a* $TBTCI(t(t+1), 3, t, 3t)$ *coexists.*

Given an $OA_I(t(t+1), 3, t+1, 2)$ with symbols from $\{0, 1, ..., t\}$, label the rows as periods, columns as units and symbols as treatments, then by definition, this OA_I is a $TBTCI(t(t+1), 3, t, 3t)$.

A Latin square of order $t+1$ with entries from $\{0, 1, 2, ..., t\}$, could be transformed into a $TBTCI(t(t+1), 3, t, 3t)$ as long as it has at least one transversal. For example:

$$\begin{array}{ccccc} \boxed{0} & 4 & 3 & 2 & 1 \\ 3 & \boxed{1} & 4 & 0 & 2 \\ 4 & 2 & 1 & \boxed{3} & 0 \\ 1 & 0 & \boxed{2} & 4 & 3 \\ 2 & 3 & 0 & 1 & \boxed{4} \end{array} \longmapsto \begin{array}{ccccc} \boxed{0} & 4 & 3 & 2 & 1 \\ 3 & \boxed{1} & 4 & 0 & 2 \\ 1 & 0 & \boxed{2} & 4 & 3 \\ 4 & 2 & 1 & \boxed{3} & 0 \\ 2 & \boxed{3} & 0 & 1 & \boxed{4} \end{array}$$

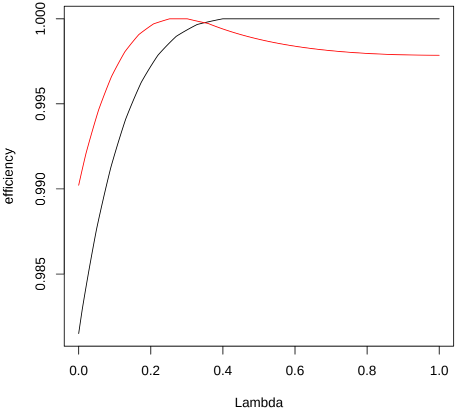
$$\longmapsto TBTCI(20, 3, 4, 12):$$

Element:	4	3	2	1	3	4	0	2	1	0	4	3	4	2	1	0	2	3	0	1
Column:	1	2	3	4	0	2	3	4	0	1	3	4	0	1	2	4	0	1	2	3
Row:	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4

Theorem

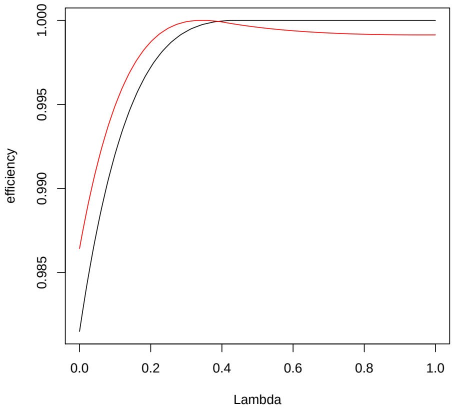
The juxtaposition of any finite collection of TBTCI's with the common number of periods and treatments would still be a TBTCI as long as we still have $|n_{d0u} - n_{d0v}| \leq 1$ *and* $|\tilde{n}_{d0u} - \tilde{n}_{d0v}| \leq 1$ *where* u *and* v *are two different subjects in the resulting design.*

$$\begin{array}{c} TBTCI(36,3,4,36) \\ \downarrow \\ TBTCI(180,3,4,180) \\ + \\ TBTCI(20,3,4,12) \\ \| \\ TBTCI(200,3,4,192) \end{array} \qquad \begin{array}{c} TBTCI(36,3,4,36) \\ \downarrow \\ TBTCI(360,3,4,360) \\ + \\ TBTCI(20,3,4,12) \\ \| \\ TBTCI(380,3,4,372) \end{array}$$



$\lambda = \theta/(1+\theta)$.

$TBTCI(180, 3, 4, 180)$ vs $TBTCI(200, 3, 4, 192)$



$\lambda = \theta/(1+\theta)$.
$TBTCI(360, 3, 4, 360)$ vs $TBTCI(380, 3, 4, 272)$

For $r_{d0} < n, p \geq 4$

Starting from the special case of $p = 5, t = 4$, we have the following 4 mutually orthogonal Latin Squares:

$$L_1: \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \\ 1 & 2 & 3 & 4 & 0 \\ 2 & 3 & 4 & 0 & 1 \\ 3 & 4 & 0 & 1 & 2 \\ 4 & 0 & 1 & 2 & 3 \end{array} \qquad L_3: \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \\ 3 & 4 & 0 & 1 & 2 \\ 1 & 2 & 3 & 4 & 0 \\ 4 & 0 & 1 & 2 & 3 \\ 2 & 3 & 4 & 0 & 1 \end{array}$$

$$L_2: \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \\ 2 & 3 & 4 & 0 & 1 \\ 4 & 0 & 1 & 2 & 3 \\ 1 & 2 & 3 & 4 & 0 \\ 3 & 4 & 0 & 1 & 2 \end{array} \qquad L_4: \begin{array}{ccccc} 0 & 1 & 2 & 3 & 4 \\ 4 & 0 & 1 & 2 & 3 \\ 3 & 4 & 0 & 1 & 2 \\ 2 & 3 & 4 & 0 & 1 \\ 1 & 2 & 3 & 4 & 0 \end{array}$$

Since L_1, L_2 and L_3 has the main diagonal as a common transversal, we rename the symbols to get the following:

$$L'_1: \begin{array}{ccccc} 0 & 3 & 1 & 4 & 2 \\ 3 & 1 & 4 & 2 & 0 \\ 1 & 4 & 2 & 0 & 3 \\ 4 & 2 & 0 & 3 & 1 \\ 2 & 0 & 3 & 1 & 4 \end{array} \quad L'_2: \begin{array}{ccccc} 0 & 2 & 4 & 1 & 3 \\ 4 & 1 & 3 & 0 & 2 \\ 3 & 0 & 2 & 4 & 1 \\ 2 & 4 & 1 & 3 & 0 \\ 1 & 3 & 0 & 2 & 4 \end{array} \quad L'_3: \begin{array}{ccccc} 0 & 4 & 3 & 2 & 1 \\ 2 & 1 & 0 & 4 & 3 \\ 4 & 3 & 2 & 1 & 0 \\ 1 & 0 & 4 & 3 & 2 \\ 3 & 2 & 1 & 0 & 4 \end{array}$$

When we go through each entry except the main diagonal, we have $TBTCI(20, 5, 4, 20)$

L'_1:	3	1	4	2	3	4	2	0	1	4	0	3	4	2	0	1	2	0	3	1
L'_2:	2	4	1	3	4	3	0	2	3	0	4	1	2	4	1	0	1	3	0	2
L'_3:	4	3	2	1	2	0	4	3	4	3	1	0	1	0	4	2	3	2	1	0
Column:	1	2	3	4	0	2	3	4	0	1	3	4	0	1	2	4	0	1	2	3
Row:	0	0	0	0	1	1	1	1	2	2	2	2	3	3	3	3	4	4	4	4

By selecting any 4 or 3 of the 5 rows of the $TBTCI(20, 5, 4, 20)$, we get $TBTCI(20, 4, 4, 16)$ or $TBTCI(20, 3, 4, 12)$ respectively.

Theorem

A type I orthogonal array $OA_I(t(t+1), p, t+1, 2)$ *and a* $TBTCI(t(t+1), p, t, pt)$ *coexists.*

Corollary

When there exits m mutually orthogonal Latin Squares of order $t+1$*, we can construct* $TBTCI(t(t+1), p, t, pt)$ *for all* $p \leq m+1$*.*

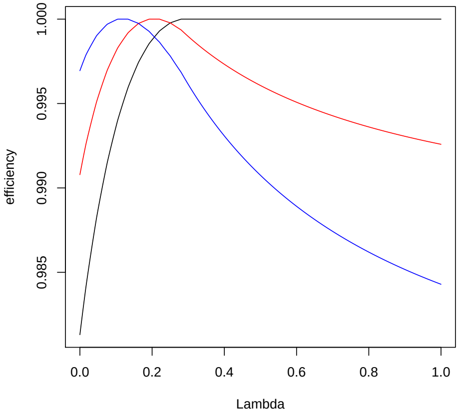
Remark: Note that $r_{d0}/n = p/(t+1)$ for the constructed designs. However these Latin Square based TBTCI designs are not optimal due to having small values of r_{d0}/n whenever $p/(t+1)$ is small. One way to rectify this problem is o jaxtapose these designs with TBTCI designs with $r_{d0}/n = 1$ — This is an open problem when $p < t$ [for $p = t, t+1$ see Hedayat and Yang (2005)]

For $r_{d0} > n, p = 4$

We can construct a $TBTCI(2t(t-1), 4, t, 4t(t-1))$ with $r_{d0}/n = 2$ as the following:
Order the units from 1 to $2t(t-1)$. For each of the first $t(t-1)$ units, assign the control treatment in periods 1 and 3, and for periods 2 and 4, use the $t(t-1)$ ordered pair of different test treatments. For each of the remaining $t(t-1)$ units, assign the control treatment in periods 2 and 4, and for periods 1 and 3, use the $t(t-1)$ ordered pair of different test treatments.

$$TBTCI(12,4,3,24): \begin{array}{cccccccccccc} 0&0&0&0&0&0&2&3&1&3&1&2\\ 2&3&1&3&1&2&0&0&0&0&0&0\\ 0&0&0&0&0&0&1&1&2&2&3&3\\ 1&1&2&2&3&3&0&0&0&0&0&0 \end{array}$$

$$\begin{array}{ccc}
TBTCI(4,4,3,4) & TBTCI(4,4,3,4) & TBTCI(4,4,3,4) \\
\downarrow & \downarrow & \downarrow \\
TBTCI(224,4,3,224) & TBTCI(212,4,3,212) & TBTCI(200,4,3,200) \\
+ & + & + \\
0 \times TBTCI(12,4,3,24) & 1 \times TBTCI(12,4,3,24) & 2 \times TBTCI(12,4,3,24) \\
\| & \| & \| \\
TBTCI(224,4,3,224) & TBTCI(224,4,3,236) & TBTCI(224,4,3,248)
\end{array}$$



$\lambda = \theta/(1+\theta)$.
$TBTCI(224, 4, 3, 248)$, $TBTCI(224, 4, 3, 236)$ and $TBTCI(224, 4, 3, 224)$.

- Construction of TBTCI designs with $r_{d0} > n$ for $p \geq 5$.
- Alternative methods of constructing TBTCI designs for cases with solutions.
- Search for optimal designs within larger class of competing designs and the related construction problems.
- Trade-off Problems

Inferences

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Thank You!