Universally Optimal Crossover Designs under Subject Dropout

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The Big Question

If subjects drop out early in an experiment, would an optimal crossover design still be optimal? If not, what could be an alternative choice?

Statistical Model

In a crossover design with p periods, t treatments, and n subjects the response is typically modeled as

$$Y_{dku} = \mu + \pi_k + \varsigma_u + \tau_{d(k,u)} + \gamma_{d(k-1,u)} + \varepsilon_{ku}, \quad (1)$$

where $\{\varepsilon_{ku}, 1 \le k \le p, 1 \le u \le n\}$ are independent with mean zero and variance σ^2. Here, Y_{dku} denotes the response from subject u in period k to which treatment $d(k,u) \in \{1,2,...,t\}$ was assigned by design d. Furthermore, μ is the general mean, π_k is the kth period effect, ς_u is the uth subject effect, $\tau_{d(k,u)}$ is the (direct) treatment effect of treatment $d(k,u)$, and $\gamma_{d(k-1,u)}$ is the carryover effect of treatment $d(k-1,u)$ that subject u received in the previous period (by convention $\gamma_{d(0,u)} = 0$).

For example:

$$\begin{matrix} 4 & 4 & 4 & 2 & 3 & 1 & 2 & 3 & 1 \\ 1 & 2 & 3 & 4 & 4 & 4 & 1 & 2 & 3 \\ 2 & 3 & 1 & 1 & 2 & 3 & 4 & 4 & 4 \end{matrix}$$

$$Y_{35} = \mu + \pi_3 + \varsigma_5 + \tau_2 + \gamma_4 + \varepsilon_{35} \quad (2)$$

Model in Matrix Form

Let $Y_d = (Y_{d11}, Y_{d21}, ..., Y_{dp1}, Y_{d12}, ..., Y_{dpn})'$, then the model could be written in matrix form as

$$Y_d = 1_{np}\mu + Z\boldsymbol{\pi} + U\boldsymbol{\varsigma} + T_d\boldsymbol{\tau} + F_d\boldsymbol{\gamma} + \boldsymbol{\varepsilon}, \quad (3)$$

where $\boldsymbol{\varepsilon} \sim (0, \sigma^2 I_{np})$. Here $\boldsymbol{\tau} = (\tau_1, ..., \tau_t)'$ is the *parameter of interest* while $\boldsymbol{\gamma} = (\gamma_1, ..., \gamma_t)'$, $\boldsymbol{\pi} = (\pi_1, ..., \pi_p)'$, and $\boldsymbol{\varsigma} = (\varsigma_1, ..., \varsigma_n)'$ are *nuisance parameters*. The matrices Z and U are fixed while T_d and F_d depend on the choice of design d. Also we have the decompositions $T_d = (T_1', ..., T_u', ..., T_n')'$ and $F_d = (F_1', ..., F_u', ..., F_n')'$, such that

$$\begin{matrix} 3 \\ 1 \\ 2 \end{matrix} \longrightarrow T_u = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{pmatrix}, F_u = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \end{pmatrix}$$

Information Matrix

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

$$C_d = T_d' pr^{\perp}([1_{np}|Z|U|F_d])T_d,$$
$$pr^{\perp}G = I - G(G'G)^{-}G',$$

Universal Optimality

(Kiefer, 1975) A design d is said to be *universally optimal* if it maximizes $\Phi(C_d)$ for any functional Φ satisfying

(C.1) Φ is concave.

(C.2) $\Phi(b_1 C_d) \ge \Phi(b_2 C_d)$ for any scaler $b_1 \ge b_2 \ge 0$.

(C.3) $\Phi(C_d) = \Phi(SC_dS')$ for any permutation matrix S.

Dropout Mechanism

Assumption 1: Once a subject drop out of the study, the probability that the subject reenter the study is zero.

By above assumption, we are able to define l_u, $1 \le u \le n$ to be the total number of periods that Subject u stayed in the experiment. Further assume

Assumption 2: The drop out mechanism is independent of the choice of design d as well as the outcome of the experiments. Moreover $\{l_u, 1 \le u \le n\}$ are iid.

Let $l = (l_1, ..., l_n)$ and $Z(l), U(l), T_d(l), F_d(l)$ be the matrices derived from Z, U, T_d, F_d by deleting the rows corresponding to missing observations. The information matrix for τ is

$$\begin{aligned} C_d(l) &= (T_d(l))' pr^{\perp}(Z(l)|U(l)|F_d(l))(T_d(l)) \\ &= C_{d11}(l) - C_{d12}(l)[C_{d22}(l)]^{-}C_{d21}(l) \quad (4) \end{aligned}$$

where

$$C_{d11}(l) = T_d(l)'OT_d(l) \quad C_{d12}(l) = T_d(l)'OF_d(l)$$
$$C_{d21}(l) = C_{d12}(l)' \qquad C_{d22}(l) = F_d(l)'OF_d(l)$$
$$O = pr^{\perp}(Z(l)|U(l))$$

The Target

Define $\phi_0(d) = \mathbb{E}\Phi(C_d(l))$, where the expectation is taken with respect to l. Our target is to maximize $\phi_0(d)$ for any Φ satisfying $(C.1) - (C.3)$.

Surrogate Target

Lemma 1: The Schur complement of a matrix $G \ge 0$ is a concave nondecreasing function of G.

$$G = \begin{pmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{pmatrix}$$

$G_{11.2} = G_{11} - G_{12}G_{22}^{-}G_{21}$ is a Schur compl. of G. By $(C.1)$, $(C.2)$, and Lemma 1, we have

$$\phi_0(d) \le \phi_1(d) = \Phi(C_d)$$
$$C_d = C_{d11} - C_{d12}C_{d22}^{-}C_{d21}$$
$$C_{dij} = \mathbb{E}C_{dij}(l), 1 \le i,j \le 2$$

Define the ϕ_i-efficiency, $i = 0, 1$, of a design d as $e_i(d) = \phi_i(d)/\phi_i(d_i^*)$, where d_i^* is an optimal design under ϕ_i. Then we have

$$e_0(d) \ge e_1(d)g(d)$$

where $g(d) = \phi_0(d)/\phi_1(d)$ is the *gap* function of d.

ϕ_1-Universal Optimality

A design d is ϕ_1-universally optimal, i.e. ϕ_1-optimal for all Φ satisfying $(C.1) - (C.3)$, iff

$$\sum_{s \in \mathcal{T}} p_s[\check{C}_{s11} + x^* \check{C}_{s12}B_t] = \frac{y^*}{t-1}B_t$$
$$\sum_{s \in \mathcal{T}} p_s[\check{C}_{s21} + x^* \check{C}_{s22}B_t] = 0$$
$$\sum_{s \in \mathcal{T}} p_s A_2(\hat{T}_s + x^* \hat{F}_s) = 0$$
$$\sum_{s \in \mathcal{T}} p_s = 1$$
$$p_s = 0, \quad s \notin \mathcal{T}$$

where

- p_s is the proportion of sequence s.
- $a_k = P(l_1 = k)$, and $a_{jk} = \sum_{i=j}^{k} a_i$.
- $\alpha_k = n^{-1}\left((n+1)a_k + a_{1,k-1}^{n+1} - a_{1k}^{n+1}\right)$.
- $\beta_k = a_k + a_{k+1,p}a_{1k}^{n} - a_{kp}a_{1,k-1}^{n}$, $1 \le k \le p$.
- B_p^k is a $p \times p$ matrix with the upper left corner filled with $I_k - J_k/k$.(Convention $B_p = B_p^p$.)
- $A_1 = \sum_{k=1}^{p} \alpha_k B_p^k \ge 0$.
- $A_2 = \sum_{k=1}^{p} \beta_k B_p^k \ge 0$.
- $\hat{T}_s = T_s B_t$ and $\hat{F}_s = F_s B_t$

$$\check{C}_{s11} = T_s'(A_1 - A_2)T_s + \hat{T}_s' A_1 \hat{T}_s$$
$$\check{C}_{s12} = T_s'(A_1 - A_2)F_s + \hat{T}_s' A_1 \hat{F}_s$$
$$\check{C}_{s22} = F_s'(A_1 - A_2)F_s + \hat{F}_s' A_1 \hat{F}_s$$

An Example

Low, Lewis, and Prescott (1999) worked on the same framework through direct search among Latin squares. When $p = t = 4$ and $n = 16$, they proposed a design which consists of two copies of two distinct 4×4 Latin squares which is denoted as d_1 here. By our theorem, the dropout mechanism $\vec{a} = (0, 0, 1/2, 1/2)$ yields d_2 as follows:

$$d_2 : \begin{matrix} 2 & 1 & 2 & 3 & 3 & 4 & 3 & 2 & 1 & 1 & 1 & 2 & 4 & 4 & 4 & 3 \\ 4 & 4 & 3 & 4 & 1 & 1 & 2 & 1 & 2 & 2 & 3 & 4 & 3 & 3 & 2 & 1 \\ 3 & 2 & 1 & 1 & 2 & 3 & 4 & 4 & 3 & 3 & 4 & 1 & 2 & 2 & 1 & 4 \\ 3 & 2 & 1 & 1 & 2 & 3 & 4 & 4 & 4 & 4 & 2 & 3 & 1 & 1 & 3 & 2 \end{matrix}$$

Φ	$\phi_0(d_2)$	$V_\Phi(d_2)$	$\tilde{e}_1(d_2)$	$g(d_2)$	$\ell(d_2)$
A	0.7058	0.05266	0.9989	0.9748	0.9738
D	0.7094	0.05129	0.9991	0.9796	0.9788
E	0.6337	0.06979	0.9848	0.8877	0.8743
T	0.7130	0.05005	0.9993	0.9843	0.9837

Table 1: Performance of d_2 under $\vec{a} = (0, 0, 1/2, 1/2)$.

The first two columns for d_1 are 0.665, 0.675, 0.553, 0.685 and 0.0722, 0.0678, 0.0904, 0.0633 respectively.

Conclusions

- The mechanism of subject dropout is formulated and the universally optimal design is derived in approximate design theory.
- It can be used to identify designs for any combination of n, p, t and any dropout probability distribution.
- Open problem: The algorithm to find the exact design is not applicable when $|\mathcal{T}|$ is too large, i.e. when p or/and t is large.

References

Low, J.L., Lewis, S.M. and Prescott, P. (1999). Statistics and Computing.
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