A General Equivalence Theorem for Crossover Designs under Generalized Linear Models

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Introduction

Crossover designs, also known as repeated measurements designs or change-over designs, have been used extensively in pharmaceutical research. With the help of Generalized Estimating Equations (GEEs), we identify locally D-optimal crossover designs for generalized linear models (GLMs). In this case, the traditional general equivalence theorem could not be used directly to check the optimality of obtained designs. In this manuscript, we fill this gap and derive a corresponding general equivalence theorem for crossover designs under generalized linear models.

Preliminary Setup

- We use generalized linear model (GLM) to describe the marginal distribution of Y_{ij} as in Liang and Zeger (1986) and let μ_{ij} denote the mean of a response Y_{ij}.
- Consider the following model, which models the marginal mean μ_{ij} for crossover trials through link function g as:

$$g(\mu_{ij}) = \eta_{ij} = \lambda + \beta_i + \tau_{d(i,j)} + \rho_{d(i-1,j)},$$

where $i = 1, \ldots, p; j = 1, \ldots, n$; λ is the overall mean, β_i represents the effect of the i^{th} period, τ_s is the direct effect due to treatment s and ρ_s is the carryover effect due to treatment s, where $s = 1, \ldots, t$.
- Instead of incorporating a random effects term, here, the mean response is modeled through the link function with an extra assumption that the responses from a particular subject are mutually correlated, while the responses from different subjects are uncorrelated.
- If the number of subjects is fixed to n and the number of periods is p, then the identified locally D-optimal design identifies the proportion of subjects assigned to a particular treatment sequence.
- A crossover design ξ can be denoted as follows:

$$\xi = \left\{ \begin{matrix} \omega_1 & \omega_2 & \ldots & \omega_k \\ p_{\omega_1} & p_{\omega_2} & \ldots & p_{\omega_k} \end{matrix} \right\},$$

where k is the number of treatment sequences involved, such that $\sum_{i=1}^{k} p_{\omega_i} = 1$, for $i = 1, \ldots, k$ and ω_j is the j^{th} treatment sequence.
- We focus on D-optimality and use the determinant of $\mathrm{Var}(\hat{\tau})$ as our objective function i.e., $\Phi(\xi) = det(\mathrm{Var}(\hat{\tau}))$. Then an optimal design ξ^* is the one which minimizes the objective function $\Phi(\xi)$ with respect to p_ω such that $\sum_{w \in \Omega} p_w = 1$.

Generalized Estimating Equations

- Instead of using maximum likelihood estimation (MLE) or ordinary least squares (OLS) to estimate the parameters we use quasi-likelihood estimation (Generalized Estimating Equations).
- The generalized estimating equations (GEE) are defined to be $\sum_{j=1}^{n} \frac{\partial \mu_j'}{\partial \theta} W_j^{-1} \left(\mathbf{Y}_j - \mu_j \right) = 0$ where $W_j = Cov(Y_j) = D_j^{1/2} C(\alpha) D_j^{1/2}$, where $D_j = diag\Big(Var(Y_{1j}), \ldots, Var(Y_{pj})\Big)$ and θ is a parameter vector.
- When true correlation of Y_j equals working correlation we have, $\mathrm{Var}(\hat{\theta}) = \left[\sum_{\omega \epsilon \Omega} n p_\omega \frac{\partial \mu_\omega'}{\partial \theta} W_\omega^{-1} \frac{\partial \mu_\omega}{\partial \theta} \right]^{-1} = M^{-1}$
- The matrix M can be written as follows:

$$\begin{aligned} M(\xi) &= \sum_{j=1}^{k} n p_{\omega_j} X_j^T G_j D_j^{-\frac{1}{2}} C(\alpha)^{-1} D_j^{-\frac{1}{2}} G_j X_j = \sum_{j=1}^{k} n p_{\omega_j} X_j^T G_j D_j^{-\frac{1}{2}} R^T R D_j^{-\frac{1}{2}} G_j X_j \\ &= \sum_{j=1}^{k} n p_{\omega_j} (R D_j^{-\frac{1}{2}} G_j X_j)^T (R D_j^{-\frac{1}{2}} G_j X_j) = \sum_{j=1}^{k} n p_{\omega_j} (X_j^*)^T (X_j^*), \end{aligned}$$

where $G_j = \mathrm{diag}\left\{ (g^{-1})'(\eta_{1j}), \ldots, (g^{-1})'(\eta_{pj}) \right\}$.
- The variance of the estimator of treatment effect is $\mathrm{Var}(\hat{\tau}) = H \mathrm{Var}(\hat{\theta}) H'$ where H is a $t \times m$ matrix and $m = p + 2t - 2$ is the total number of parameters in θ.

The General Equivalence Theorem

The General Equivalence Theorem states the equivalence of the following three conditions on ξ^*:

1. The design ξ^* minimizes $\Phi(\xi)$,
2. The design ξ^* maximizes the minimum over Ω of $\phi(x, \xi)$,
3. The minimum over Ω of $\phi(x, \xi)$ is 0, which occurs at the support points of the design,

where $\phi(x, \xi)$ is the directional derivative of $\Phi(\xi)$ and Ω is a set of all possible treatment sequences.

The General Equivalence Theorem can be viewed as a consequence of the result that the derivative of a smooth function over an unconstrained region is zero at its minimum.

In the case of crossover designs and estimates using generalized estimating equations, we need to take a different approach compared to the traditional one as the design points are finite and pre-specified for crossover designs.

The outline of the General Equivalence Theorem in the case of crossover designs is as follows:

- Define $p_r = (p_1, \ldots, p_{k-1})'$, and $\Phi(p_r) = \ln det(HM^{-1}(p_1, \ldots, p_{k-1}, 1 - \sum_{i=1}^{k-1} p_i)H')$. Let $\delta_i^{(r)} = (-p_1, \ldots, -p_{i-1}, 1 - p_i, -p_{i+1}, \ldots, -p_{k-1})'$ for $i = 1, \ldots, k-1$.
- Instead of using traditional way of defining direction $\xi_i' = (1-h)\xi + h\bar{\xi}_i = \xi + h(\bar{\xi}_i - \xi)$, we used $p_r + u\delta_i^{(r)}$ where h is replaced with u and $(\bar{\xi}_i - \xi)$ is replaced with $\delta_i^{(r)}$.
- Note that $0 \leq p_i < 1$ for $i = 1, \ldots, k$, and since $\sum_{i=1}^{k} p_i = 1$ we may assume without any loss of generality that $p_k > 0$.
- $\delta_i^{(r)}$ are defined in such a way that the determinant $|(\delta_1^{(r)}, \ldots, \delta_{k-1}^{(r)})| = p_k \neq 0$. Hence, $\delta_1^{(r)}, \ldots, \delta_{k-1}^{(r)}$ are linearly independent and thus can serve as the new basis of

$$S_r = \{(p_1, \ldots, p_{k-1})' | \sum_{i=1}^{k-1} p_i < 1, \text{and } p_i \geq 0, i = 1, \ldots, k-1\}.$$

- $\Phi(p_r)$ is minimized w.r.t p_r if and only if along each direction δ_i^r,

$$\left. \frac{\partial \Phi(p_r + u\delta_i^{(r)})}{\partial u} \right|_{u=0} \begin{cases} = 0 \text{ if } p_i > 0 \\ \geq 0 \text{ if } p_i = 0. \end{cases}$$

Equivalence Theorems for Crossover Designs

Theorem 1. ***(General Equivalence Theorem when objective function is $Var(\hat{\theta})$):*** *Consider the design ξ with k treatment sequences as shown earlier. Then the design ξ is D-optimal if and only if*

$$trace\left(X_i^* M(\xi)^{-1} X_i^{*T}\right) \begin{cases} = m \text{ if } p_i > 0 \\ \leq m \text{ if } p_i = 0 \end{cases}$$

for each $p_i \in [0, 1]$, where p_i is the allocation corresponding to point ω_i of design ξ for all $i = 1, 2, \ldots, k$, and m is the number of parameters in θ.

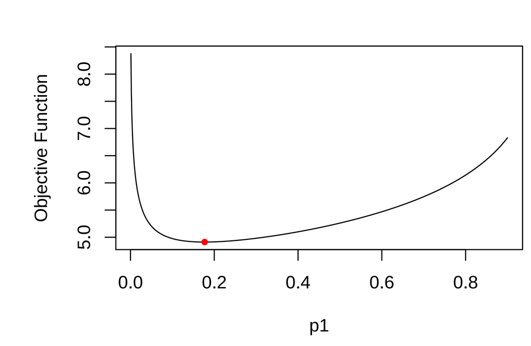
Theorem 2. ***(General Equivalence Theorem when objective function is $Var(\hat{\tau})$):*** *Consider the design ξ with k treatment sequences as shown earlier. Then the design ξ is D-optimal if and only if*

$$trace\left\{A(X_i^*)^T(X_i^*)\right\} \begin{cases} = t - 1 \text{ if } p_i > 0 \\ \leq t - 1 \text{ if } p_i = 0 \end{cases}$$

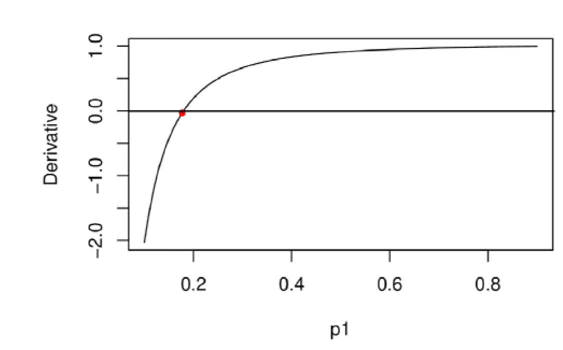
for each $p_i \in [0, 1]$, where $A = M^{-1}H'\left(HM^{-1}H'\right)^{-1}HM^{-1}$, p_i is the allocation corresponding to point ω_i of design ξ for all $i = 1, 2, \ldots, k$, and t is number of treatments.

Illustration

- To illustrate the results of above general equivalence theorems, we consider a design space $\{AB, BA\}$ which is a case of $k = 2, p = 2$.
- For the assumed θ and $\Phi(p_1) = \ln det(HM^{-1}(p_1)H')$ as the objective function, the obtained optimal proportions are $p_1 = 0.177$ and $p_2 = 0.823$.



Objective Function: $\Phi(p_1) = \ln det(HM^{-1}(p_1)H')$.

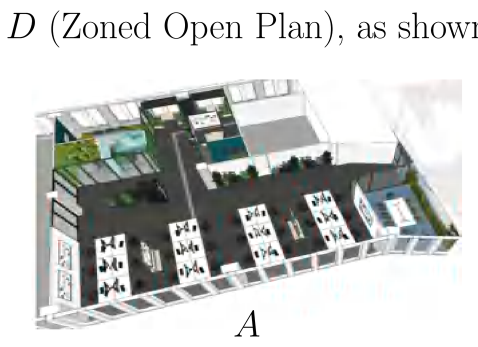


Derivative: $trace\left\{A(X_1^*)^T(X_1^*)\right\} - (t-1)$

- We can see from the left panel in figure that the minimum of the objective function is located at $p_1 = 0.177$, which suggests us that obtained proportions are indeed optimal and they produce the D-optimal design when the objective function is $Var(\hat{\tau})$.

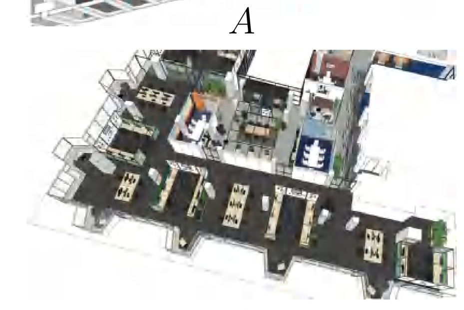
Real Example: Work Environment Experiment

- In this example we consider the data obtained from the work environment experiment conducted at Booking.com.
- There were no previous studies to examine the effects of office designs in work spaces, Booking.com conducted an experiment to assess different office spacing efficiency.
- This experiment is essentially a uniform crossover design with $p = 4$ periods and $t = 4$ treatments and the four treatments involved in this experiment are office designs named as A (Activity-Based), B (Open Plan), C (Team Offices), and D (Zoned Open Plan), as shown in the figure below:

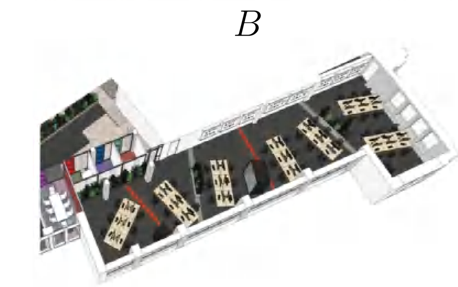


A

B



C



D

- A Latin square design of order four has been used to determine the sequence of exposure so that no group was exposed to the conditions in the same order as any other group.
- During the course of experiment many different responses were recorded. For the illustration purpose we consider the response *commit count* to illustrate the optimal crossover design for the Poisson response.
- According to Theorem 2, when $Var(\hat{\theta})$ is the objective function, the D-optimal design can be obtained by solving the system of equations below instead of performing constrained optimization to attain the minimum of the objective function. The system of equations is as follows:

$$\mathrm{trace}\left(X_i^* M(p_r)^{-1} X_i^{*T}\right) = 10,$$

for $i = 1, 2, 3, 4$.
- The obtained design is the same as the one obtained by performing constrained optimization, which implies that the design is indeed optimal.

Conclusions

- In this paper, we derive an expression for general equivalence theorem to check for the optimality of identified locally D-optimal crossover designs for generalized linear models.
- The equivalence theorem provides us with a system of equations that can calculate optimal proportions with more ease without performing constrained optimization of the objective function.

References

- Jankar, J.; Yang, J. and Mandal, A. (2021). "A General Equivalence Theorem for Crossover Designs under Generalized Linear Models", to be submitted.