On the design of experiments with ordered experimental treatments

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Applications

- In dose–response studies, responses are increasing with increasing amount of dose (Simple order).
- In clinical trials, a placebo or control group is tested against multiple treatment groups (Tree order).
- Multiple controls versus multiple treatments comparisons (Bipartite order).
- Referred to [Barlow et al., 1972] for more applications.

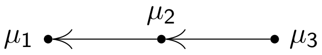
Case studies: Simple order

- In the study by [Spiegelhalter et al., 1999] the height of the ramus bone was measured at three equally spaced time points for 20 boys ages 8 to 9. The goal of the study was to identify significant growth spurts, i.e., to test for $\mu_1 \leq \mu_2 \leq \mu_3$, with at least one strict inequlity.

- Sample means: $\hat{\boldsymbol{\mu}} = (\hat{\mu}_1, \hat{\mu}_2, \hat{\mu}_3) = (48.66, 49.62, 50.57)$

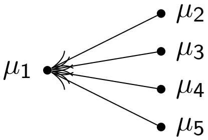
- Design: $\boldsymbol{n} = (n_1, n_2, n_3) = (20, 20, 20)$, Balanced design ?

- Graph:



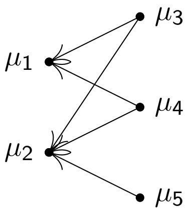
Case studies: Tree order

- [Igari et al., 2014] investigated the effect of various drugs on dysporic-like state in rats. In particular, different doses of cytisine (drug used for smoking cessation treatment) are given to the rats and associated intracranial self-stimulation (ICSS) thresholds are observed (response). ICSS measures the potentiation of brain reward function.
- Sample means: $\hat{\boldsymbol{\mu}} = (\hat{\mu}_1, \ldots, \hat{\mu}_5) = (97.6, 101.6, 102.2, 103.4, 105.9)$
- Design: $\boldsymbol{n} = (n_1, \ldots, n_5) = (12, \ldots, 12)$, Balanced design ?
- Graph:



Case studies: Bipartite order

- The study by [Blake and Boockfor, 1997] designed to study the effect of 4-Tert-Octylphenol (OP) on reproductive hormone secretion in the adult male rats.
- The outcome is the ratio of organ (the left kidney) to body weight.
- Two control groups (injection of corn oil, no injection) and four treatment groups with varied doses of OP and estradiol valerate.



Case studies: Bipartite order

- Sample means: $\hat{\boldsymbol{\mu}} = (\hat{\mu}_1, \ldots, \hat{\mu}_5) = (3.78, 3.60, 3.96, 4.06, 3.68)$
- Design: $\boldsymbol{n} = (n_1, \ldots, n_5) = (6, \ldots, 6)$, Balanced design ?

Stress to

"Customize the experiment for the setting instead of adjusting the setting to fit a classical design".

Smucker, B., Krzywinski, M. and Altman, N.: Optimal experimental design. *Nature Methods* 15, 557–560 (2018)

Model

Suppose there are K treatment groups and n_i subjects to the ith group.

- *One-way ANOVA:*

$$Y_{ij} = \mu_i + \epsilon_{ij}, \quad i = 1, \ldots, K \text{ and } j = 1, \ldots, n_i$$

  - Y_{ij}:response of j^{th} subject in i^{th} treatment group
  - μ_i: ith treatment effect
  - $\epsilon_{ij} \sim N(0, \sigma^2)$.

Order restrictions

- In dose response experiments one often expects an increasing response with an increasing dose.

$$\text{Simple Order} : \mu_1 \leq \mu_2 \leq \cdots \leq \mu_K$$

- Comparing several treatments with a control.

$$\text{Tree Order} : \mu_1 \leq [\mu_2, \ldots, \mu_K]$$

- Investigate and localize the age at which learning ability peaks.

$$\text{Umbrella Order} : \mu_1 \leq \cdots \leq \mu_h \geq \cdots \geq \mu_K$$

In General,

$$\mathcal{M}_1 = \{\boldsymbol{\mu} \in \mathbb{R}^K : \boldsymbol{R}\boldsymbol{\mu} \geq 0\},$$

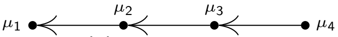
matrix $\boldsymbol{R}$ with elements $r_{ij} \in \{-1, 0, 1\}$, referred to as restriction matrix.

Objective

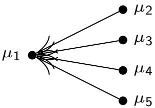
The existing methods for designing experiments in the presence of an ordering are limited in scope. A broad understanding and formal methods, for constructing optimal designs under order restrictions are still lacking. Our objective is to:

- Introducing a new maxi–min optimality criteria tailored for testing hypotheses;
- Using this criteria to derive optimal designs for u–LRTs, r–LRTs and Intersection-Union-Tests (IUTs); and
- Exploring the relations between the proposed designs and some other well known design criteria.

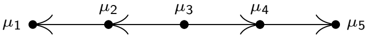
Graphical Representation



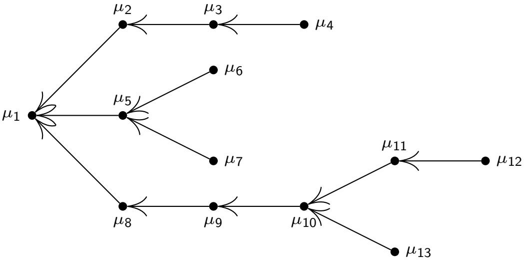
(a) Simple order



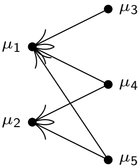
(b) Simple tree order



(c) Umbrella order



(d) Complex tree order

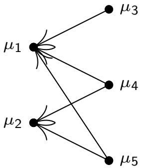


(e) Bipartite order

Graphical Representation

- Let $\mathcal{R}$ and $\mathcal{L}$ denote, respectively, the set of roots and leafs of an order graph.
- The pair (i, j) where $i \in \mathcal{R}$ and $j \in \mathcal{L}$ is called a *maximal pair* if there is a path from i to j.
- The degree of the vertex i, denoted by d_i, is the number of directed edges connected to it.
- Let $\mathcal{V}$ denotes the set of maximal pairs with cardinality $|\mathcal{V}|$.

Graphical Representation



(a) Bipartite order

$\mathcal{L} = \{1, 2\}$, $\mathcal{R} = \{3, 4, 5\}$, $d_1 = 3, d_2 = 2, d_3 = 1, d_4 = 2, d_5 = 2,$
$\mathcal{V} = \{(1, 3), (1, 4), (1, 5), (2, 4), (2, 5)\}$, $|\mathcal{V}| = 5.$

Tests

- Hypothesis

$$H_0 : \boldsymbol{\mu} \in \mathcal{M}_0 \quad \text{versus} \quad H_1 : \boldsymbol{\mu} \in \mathcal{M}_1 \setminus \mathcal{M}_0,$$

  where $\mathcal{M}_0 = \{\boldsymbol{\mu} \in \mathbb{R}^K : \mu_1 = \mu_2 = \cdots = \mu_K\}$.
- The LRT statistic is:

$$T_n = 2 \log \left\{ \frac{\max_{\boldsymbol{\mu} \in \mathcal{M}_1} L(\boldsymbol{\mu})}{\max_{\boldsymbol{\mu} \in \mathcal{M}_0} L(\boldsymbol{\mu})} \right\}$$

  where

$$L(\boldsymbol{\mu}) = \prod_{i=1}^{K} \prod_{j=1}^{n_i} (\sqrt{2\pi})^{-1/2} \exp\{-\frac{1}{2}(Y_{ij} - \mu_i)^2\}$$

  .

Tests

- u–LRT (standard ANOVA): $H_1 : \boldsymbol{\mu} \notin \mathcal{M}_0$.
- u–LRT: T_n follows a chi–square distribution.
- r–LRT: $H_1 : \boldsymbol{\mu} \in \mathcal{M}_1 \setminus \mathcal{M}_0$.
- r–LRT: T_n follows a chi–bar–square distribution ([Robertson et al., 1988]).

Approximate Design

- Exact design: $\mathcal{N} = \{(n_1, n_2, \ldots, n_K) : n_i \geq 0, \sum_{i=1}^{K} n_i = N\}$ denote the set of all possible ways of arranging N subjects in K groups.

- Approximate design: denoted by $\boldsymbol{\xi}$, where $\boldsymbol{\xi} = \{(\xi_1, \xi_2, \ldots, \xi_K)^T\} \in \Xi$ is a vector of probabilities and the design space Ξ is the unit simplex i.e., $\xi_i \geq 0$ and $\sum_{i=1}^{K} \xi_i = 1$. Basically, $\boldsymbol{\xi}_i = n_i/N$, for $i = 1, \ldots, K$.

- The power function

$$\pi(\boldsymbol{\mu}; \boldsymbol{\xi}) = \mathbb{P}_{\boldsymbol{\mu},\boldsymbol{\xi}}(T_n \geq c_{\alpha,\boldsymbol{\xi}}) = \sum_{j=0}^{K} w_j \mathbb{P}(\chi_j^2 \geq c)$$

depends on $\boldsymbol{\mu}$, $\boldsymbol{\xi}$ and $w_j = w_j(\Sigma, \mathcal{M}_1)$ are non-negative weights summing to unity and $\Sigma = \text{diag}(N/n_1, \ldots, N/n_K)$.

Motivation: A power maximizing design

Theorem

If $|\mu_i - \mu_j| = \max\{|\mu_s - \mu_t| : 1 \leq s, t \leq K\}$ *then an optimal design for standard ANOVA is* $\xi_{\text{opt}} = (1/2)(e_i + e_j)$, *where* e_l *is the* l^{th} *standard basis of* $\mathbb{R}^K$.

Prior to the experiment, it is not know that which pair (i, j) of treatments is maximally separated.

Example

For $\boldsymbol{\mu}_1 = (1, -1, 0, 0)$, then $\boldsymbol{\xi}_1 = (1/2, 1/2, 0, 0)$ is optimal. For $\boldsymbol{\mu}_2 = (0, 0, -1, 1)$, then $\boldsymbol{\xi}_2 = (0, 0, 1/2, 1/2)$ is optimal. Then $\pi_{\boldsymbol{\xi}_1, \boldsymbol{\mu}_1} = \pi_{\boldsymbol{\xi}_2, \boldsymbol{\mu}_2} = 1$ as $N \to \infty$ but $\pi_{\boldsymbol{\xi}_2, \boldsymbol{\mu}_1} = \pi_{\boldsymbol{\xi}_1, \boldsymbol{\mu}_2} = \alpha$ as $N \to \infty$.

Design Selection Criterion

Define $\boldsymbol{\xi}_{\mathrm{MM}}$ and $\boldsymbol{\mu}_{\mathsf{LFC}}$ as the the values satisfying:

$$\pi(\boldsymbol{\mu}_{\mathsf{LFC}}; \boldsymbol{\xi}_{\mathrm{MM}}) = \max_{\boldsymbol{\xi}} \min_{\boldsymbol{\mu}} \pi(\boldsymbol{\mu}; \boldsymbol{\xi}), \tag{1}$$

where $\boldsymbol{\xi} \in \Xi$ and $\boldsymbol{\mu} \in \mathcal{M}_\delta \subset \mathcal{M}_1 \setminus \mathcal{M}_0$ where δ measures the distance from the null.

Parameter space:

$$\mathcal{M}_\delta = \{\boldsymbol{\mu} \in \mathbb{R}^K : \boldsymbol{I}\boldsymbol{\mu} \geq 0, \boldsymbol{R}\boldsymbol{\mu} \geq 0, \sum_{(i,j)\in\mathcal{V}} (\mu_i - \mu_j) \geq \delta\}. \tag{2}$$

We refer to $\boldsymbol{\xi}_{\mathrm{MM}}$ as the maxi–min design (MM–design), and $\boldsymbol{\mu}_{\mathsf{LFC}}$ as the least favorable configuration (LFC).

Remark

The constraint in (2) in a 1–norm. More generally a κ–norm would lead to a constraint of the type $\sum_{(i,j)\in\mathcal{V}}(\mu_i - \mu_j)^\kappa)^{1/\kappa} \geq \delta$. For example, when $\kappa = 2$ the sum $\sum_{(i,j)\in\mathcal{V}}(\mu_i - \mu_j)^2$ can be rewritten as $\boldsymbol{\mu}^T \boldsymbol{L}\boldsymbol{\mu}$ where $\boldsymbol{L}$ is the Laplacian matrix of the order graph; whereas when $\kappa \to \infty$ we obtain the constraint $\max_{(i,j)\in\mathcal{V}}(\mu_i - \mu_j) \geq \delta$. A little thought reveals that κ plays no role in the minimization of the power function over $\mathcal{M}_\delta$ and therefore for simplicity we set $\kappa = 1$.

Results: u–LRT (ANOVA)

Theorem

The balanced design is the maxi-min design in the standard ANOVA setting.

Theorem

For any order graph the MM–design for the u–LRT is given by:

$$\xi_{\mathrm{MM}} = |\mathcal{V}|^{-1} \sum_{(i,j)\in\mathcal{V}} \xi_{ij}, \text{ where } \xi_{ij} = (\boldsymbol{e}_i + \boldsymbol{e}_j)/2.$$

Further simplifies to

$$\xi_{\mathrm{MM}} = (2|\mathcal{V}|)^{-1}(t_1, \ldots, t_K),$$

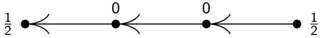
where $t_i = d_i$ if $i \in \mathcal{L} \cup \mathcal{R}$ and 0 otherwise.

Sketch of the proof:

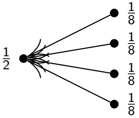
- Non-centrality parameter (NCP) versus Power.
- Reduction of general order graph to Bipartite order.
- Equivalence Theorem.

Corollary

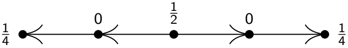
The designs: (i) $(e_1 + e_K)/2$*; (ii)* $e_1/2 + \sum_{i=2}^{K} e_i/(2(K-1))$*; and (iii)* $e_h/2 + (e_1 + e_K)/4$ *are the MM–designs for the simple, tree and umbrella (with a peak at h) order, respectively.*



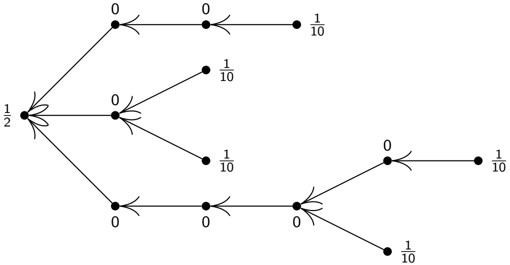
(b) Simple order



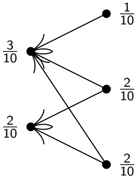
(c) Simple tree order



(d) Umbrella order



(e) Complex tree order



(f) Bipartite order

Figure: MM–designs for various order restrictions

r–LRT

Theorem

The design $(e_1 + e_K)/2$ is the MM–design for the r–LRT under the simple order.

Theorem

For any order graph and as $N \to \infty$ the MM–design for the r–LRT satisfies

$$\xi_{\mathrm{MM}}^{\mathrm{R}} = \xi_{\mathrm{MM}}^{\mathrm{U}} + o(1).$$

Results

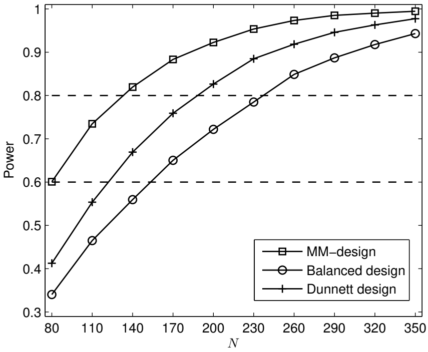


Figure: The power of the u–LRT based on balanced and Dunnett designs and the powers of the r–LRT based on the MM–design for tree order with $K = 4$

Results: Simulated

Table: The required sample sizes (N) necessary to achieve pre-specified power based on the r–LRT. The MM, balanced, Dunnett and Singh designs are compared under the tree order with $K = 4$ and $K = 5$. The reduction in sample size due to the MM design are reported in (%).

	$N(K=4)$				$N(K=5)$		
Power	MM	Balanced	Dunnett	Singh	MM	Balanced	Dunnett
60%	78	112 (44%)	88 (13%)	86 (10%)	87	149 (71%)	104 (19.5%)
80%	130	185 (42%)	145 (11.5%)	140 (7.7%)	139	239 (72%)	164 (18%)

Results: Real data examples

Table: Sample size N required to achieve a 80% power based on r–LRT.

Case Study		Simple order	Tree order (a)	Bipartite order
Design	MM	42	99	280
	Balanced	66	140	320
	Dunnett's	–	110	–

Further work...

- Do not assign observations to the intermediate group.
- As a solution, we also proposed designs based on Intersection Union Tests (IUTs).
- MM–design are Bayes design with respect to the least favourable prior of $\boldsymbol{\mu}$.
- MM–design is Nash design associated with the Game theoritic framework of the usual ANOVA.

Future work

- Designs for experiments with co-variates models.
- Correlated observations.
- Generalized linear models.

Thank

- You: for your attention.
- Questions and Suggestions?

Barlow, R. E., Bartholomew, D. J., Bremner, J. M., and Brunk, H. D. (1972).
Statistical Inference under Order Restrictions.
Wiley, New York.

Blake, C. A. and Boockfor, F. R. (1997).
Chronic administration of the environmental pollutant 4-tert-octylphenol to adult male rats interferes with the secretion of luteinizing hormone, follicle-stimulating hormone, prolactin, and testosterone.
Biology of Reproduction, 57:255–266.

Igari, M., Alexander, J. C., Ji, Y., Xiaoli, Q., Papke, R. L., and Bruijnzeel, A. W. (2014).
Varenicline and cytisine diminish the dysphoric-like state associated with spontaneous nicotine withdrawal in rats.
Neuropsychopharmacology, 39:445–455.

Robertson, T., Wright, F. T., and Dykstra, R. L. (1988).
Order Restricted Statistical Inference.

Wiley, New York.

Spiegelhalter, D., Thomas, A., Best, N., and Gilks, W. (1999).
BUGS 0.5 Examples volume 2, MRC biostatistics Unit.
Institute of Public Health. Robinson Way, Cambridge CB2 2SR.