Screening Active Dispersion Effects from Unreplicated Order-of-Addition Experiments

單一重複添加次序試驗之分散效應篩選

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July 14, 2023

Outline

- Background
- The proposed method
- Simulation studies
- Real data analysis
- Group-wise exchange algorithm
- Summary

A drug combination experiment

- Four drugs are added sequentially to the human lymphoma cell, and the cell inhibition rate was measured

h	t_h	y_h
1	1234	27.31
2	1342	37.30
3	1423	24.42
4	2143	23.30
5	2314	29.29
6	2431	26.01
7	3124	35.98
8	3241	39.48
9	3412	36.78
10	4132	33.16
11	4213	25.81
12	4321	31.17

- Absence of factors
- The conventional statistical method cannot be applied

Order-of-Addition Experiments

- To study the impact of responses with various addition orders of materials
- Components: materials of interest
- The hth treatment $\boldsymbol{t}_h$: a permutation of m components
- The pairwise order factor

$$z_{h,ij} = \begin{cases} +1 & \text{if component } i \text{ is added before component } j \text{ in } \boldsymbol{t}_h; \\ -1 & \text{if component } i \text{ is added after component } j \text{ in } \boldsymbol{t}_h. \end{cases}$$

- For example:
  There are three components: 1, 2, and 3

$\boldsymbol{t}_h$	$z_{h,12}$	$z_{h,13}$	$z_{h,23}$
213	-1	$+1$	$+1$
132	$+1$	$+1$	-1

Motivation

- The addition order of components may have a significant impact on
  - the response mean $\rightarrow$ Location effects
  - the response variance $\rightarrow$ Dispersion effects
- Dispersion effects play a vital role in quality control
- It is crucial to identify the dispersion effects

The Proposed Method

- Screen active dispersion effect from unreplicated order-of-addition experiments
- With several important steps
  1. Remove the impact of active location effects
  2. Determine a requirement set
  3. Remove the impact of nuisance parameters
  4. Screen active dispersion effects

1.Removing the Impact of Active Location Effects

- Assume the response of $\boldsymbol{t}_h$

$$Y_h \sim N(\mu_h, \sigma_h^2)$$

- Location effects model

$$\mu_h = \gamma_0 + \sum_{ij \in \mathcal{L}} \gamma_{ij} z_{h,ij}$$

- $\mathcal{L}$ collects the indices of all active location effects
- Assume that

$$\gamma_{ij} = 0 \text{ for } ij \notin \mathcal{L}$$

- Use stepwise regression to screen active location effects

2.Determining a Requirement Set $\mathcal{D}$

- Dispersion effects model

$$\sigma_h^2 = \delta_0 \prod_{ij \in \mathcal{D}} \delta_{ij}^{\frac{z_{h,ij}}{2}}$$

- Collect potentially active dispersion effects in $\mathcal{D}$
- $\mathcal{D}$ is determined based on prior knowledge or residual diagnosis tools
- Test $H_0 : \delta_{ij} = 1$ for each $ij \in \mathcal{D}$
- The design is split into s groups according to $\mathcal{D}$

$$\mathcal{I}_g = \{h \mid \boldsymbol{z}_h^* = \boldsymbol{w}_g\}$$

Example 1

The 16-run order-of-addition design with $\mathcal{D} = \{12, 13, 14\}$

h	$\boldsymbol{t}_h$	$z_{h,12}$	$z_{h,13}$	$z_{h,14}$	$z_{h,23}$	$z_{h,24}$	$z_{h,34}$
1	1234	$+1$	$+1$	$+1$	$+1$	$+1$	$+1$
2	1243	$+1$	$+1$	$+1$	$+1$	$+1$	-1
3	2134	-1	$+1$	$+1$	$+1$	$+1$	$+1$
4	2143	-1	$+1$	$+1$	$+1$	$+1$	-1
5	2314	-1	-1	$+1$	$+1$	$+1$	$+1$
6	2341	-1	-1	-1	$+1$	$+1$	$+1$
7	2413	-1	$+1$	-1	$+1$	$+1$	-1
8	2431	-1	-1	-1	$+1$	$+1$	-1
9	3124	$+1$	-1	$+1$	-1	$+1$	$+1$
10	3142	$+1$	-1	$+1$	-1	-1	$+1$
11	3214	-1	-1	$+1$	-1	$+1$	$+1$
12	3412	$+1$	-1	-1	-1	-1	$+1$
13	4123	$+1$	$+1$	-1	$+1$	-1	-1
14	4132	$+1$	$+1$	-1	-1	-1	-1
15	4213	-1	$+1$	-1	$+1$	-1	-1
16	4312	$+1$	-1	-1	-1	-1	-1

Example 1

$\mathcal{D} = \{12, 13, 14\}$ $\quad$ $\boldsymbol{z}_h^* = \begin{bmatrix} z_{h,12} & z_{h,13} & z_{h,14} \end{bmatrix}^\top$

h	$\boldsymbol{t}_h$	$z_{h,12}$	$z_{h,13}$	$z_{h,14}$	$z_{h,23}$	$z_{h,24}$	$z_{h,34}$
1	1234	+1	+1	+1	+1	+1	+1
2	1243	+1	+1	+1	+1	+1	−1
3	2134	−1	+1	+1	+1	+1	+1
4	2143	−1	+1	+1	+1	+1	−1
5	2314	−1	−1	+1	+1	+1	+1
6	2341	−1	−1	−1	+1	+1	+1
7	2413	−1	+1	−1	+1	+1	−1
8	2431	−1	−1	−1	+1	+1	−1
9	3124	+1	−1	+1	−1	+1	+1
10	3142	+1	−1	+1	−1	−1	+1
11	3214	−1	−1	+1	−1	+1	+1
12	3412	+1	−1	−1	−1	−1	+1
13	4123	+1	+1	−1	+1	−1	−1
14	4132	+1	+1	−1	−1	−1	−1
15	4213	−1	+1	−1	+1	−1	−1
16	4312	+1	−1	−1	−1	−1	−1

$\boldsymbol{w}_1$	−1	−1	−1
$\boldsymbol{w}_2$	−1	−1	+1
$\boldsymbol{w}_3$	−1	+1	−1
$\boldsymbol{w}_4$	−1	+1	+1
$\boldsymbol{w}_5$	+1	−1	−1
$\boldsymbol{w}_6$	+1	−1	+1
$\boldsymbol{w}_7$	+1	+1	−1
$\boldsymbol{w}_8$	+1	+1	+1

Example 1

$$\boldsymbol{z}_6^* = \boldsymbol{z}_8^* = \boldsymbol{w}_1 = \begin{bmatrix} -1 & -1 & -1 \end{bmatrix}^\top \rightarrow \mathcal{I}_1 = \{6, 8\}$$

h	$\boldsymbol{t}_h$	$z_{h,12}$	$z_{h,13}$	$z_{h,14}$	$z_{h,23}$	$z_{h,24}$	$z_{h,34}$
1	1234	$+1$	$+1$	$+1$	$+1$	$+1$	$+1$
2	1243	$+1$	$+1$	$+1$	$+1$	$+1$	-1
3	2134	-1	$+1$	$+1$	$+1$	$+1$	$+1$
4	2143	-1	$+1$	$+1$	$+1$	$+1$	-1
5	2314	-1	-1	$+1$	$+1$	$+1$	$+1$
6	2341	-1	-1	-1	$+1$	$+1$	$+1$
7	2413	-1	$+1$	-1	$+1$	$+1$	-1
8	2431	-1	-1	-1	$+1$	$+1$	-1
9	3124	$+1$	-1	$+1$	-1	$+1$	$+1$
10	3142	$+1$	-1	$+1$	-1	-1	$+1$
11	3214	-1	-1	$+1$	-1	$+1$	$+1$
12	3412	$+1$	-1	-1	-1	-1	$+1$
13	4123	$+1$	$+1$	-1	$+1$	-1	-1
14	4132	$+1$	$+1$	-1	-1	-1	-1
15	4213	-1	$+1$	-1	$+1$	-1	-1
16	4312	$+1$	-1	-1	-1	-1	-1

$\boldsymbol{w}_1$	-1	-1	-1
$\boldsymbol{w}_2$	-1	-1	$+1$
$\boldsymbol{w}_3$	-1	$+1$	-1
$\boldsymbol{w}_4$	-1	$+1$	$+1$
$\boldsymbol{w}_5$	$+1$	-1	-1
$\boldsymbol{w}_6$	$+1$	-1	$+1$
$\boldsymbol{w}_7$	$+1$	$+1$	-1
$\boldsymbol{w}_8$	$+1$	$+1$	$+1$

Example 1

- Given $\mathcal{D} = \{12, 13, 14\}$
- The design is split into 8 groups
  - $\mathcal{I}_1 = \{6, 8\}$
  - $\mathcal{I}_2 = \{5, 11\}$
  - $\mathcal{I}_3 = \{7, 15\}$
  - $\mathcal{I}_4 = \{3, 4\}$
  - $\mathcal{I}_5 = \{12, 16\}$
  - $\mathcal{I}_6 = \{9, 10\}$
  - $\mathcal{I}_7 = \{13, 14\}$
  - $\mathcal{I}_8 = \{1, 2\}$
- Responses within $\mathcal{I}_g$ have the same variance
- $\mathcal{I}_1 \longrightarrow SSE_1, \mathcal{I}_2 \longrightarrow SSE_2, \dots, \mathcal{I}_s \longrightarrow SSE_s$

3.Removing the Impact of Nuisance Parameters

- When testing $H_0 : \delta_{st} = 1$
- The remaining dispersion effects indexed by $\mathcal{D} \setminus \{st\}$ are nuisance parameters
- The concept of quasi-foldover pairs (a, b) is defined to remove the impact of nuisance parameters

Definition 1

$$\mathcal{P}_{st} = \{(a, b) \mid w_{a,st} = w_{b,st} = +1 \text{ and } w_{a,ij} + w_{b,ij} = 0 \\ \text{for each } ij \in \mathcal{D} \setminus \{st\}\}$$

$$\mathcal{N}_{st} = \{(a, b) \mid w_{a,st} = w_{b,st} = -1 \text{ and } w_{a,ij} + w_{b,ij} = 0 \\ \text{for each } ij \in \mathcal{D} \setminus \{st\}\}$$

Example 2

Given a requirement set $\mathcal{D} = \{12, 13, 14\}$, there are eight $(+1, -1)$-vectors

$$
\begin{aligned}
\boldsymbol{w}_1^\top &= \begin{bmatrix} -1 & -1 & -1 \end{bmatrix}, & \boldsymbol{w}_2^\top &= \begin{bmatrix} -1 & -1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_3^\top &= \begin{bmatrix} -1 & +1 & -1 \end{bmatrix}, & \boldsymbol{w}_4^\top &= \begin{bmatrix} -1 & +1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_5^\top &= \begin{bmatrix} +1 & -1 & -1 \end{bmatrix}, & \boldsymbol{w}_6^\top &= \begin{bmatrix} +1 & -1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_7^\top &= \begin{bmatrix} +1 & +1 & -1 \end{bmatrix}, & \boldsymbol{w}_8^\top &= \begin{bmatrix} +1 & +1 & +1 \end{bmatrix}.
\end{aligned}
$$

- $\mathcal{P}_{12} = \{(5, 8), (6, 7)\}$,

Example 2

Given a requirement set $\mathcal{D} = \{12, 13, 14\}$, there are eight $(+1, -1)$-vectors.

$$
\begin{aligned}
\boldsymbol{w}_1^\top &= \begin{bmatrix} -1 & -1 & -1 \end{bmatrix}, & \boldsymbol{w}_2^\top &= \begin{bmatrix} -1 & -1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_3^\top &= \begin{bmatrix} -1 & +1 & -1 \end{bmatrix}, & \boldsymbol{w}_4^\top &= \begin{bmatrix} -1 & +1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_5^\top &= \begin{bmatrix} +1 & -1 & -1 \end{bmatrix}, & \boldsymbol{w}_6^\top &= \begin{bmatrix} +1 & -1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_7^\top &= \begin{bmatrix} +1 & +1 & -1 \end{bmatrix}, & \boldsymbol{w}_8^\top &= \begin{bmatrix} +1 & +1 & +1 \end{bmatrix}.
\end{aligned}
$$

- $\mathcal{P}_{12} = \{(5, 8), (6, 7)\}$, $\mathcal{N}_{12} = \{(1, 4), (2, 3)\}$

Example 2

Given a requirement set $\mathcal{D} = \{12, 13, 14\}$, there are eight $(+1, -1)$-vectors.

$$
\begin{aligned}
\boldsymbol{w}_1^\top &= \begin{bmatrix} -1 & -1 & -1 \end{bmatrix}, \quad & \boldsymbol{w}_2^\top &= \begin{bmatrix} -1 & -1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_3^\top &= \begin{bmatrix} -1 & +1 & -1 \end{bmatrix}, \quad & \boldsymbol{w}_4^\top &= \begin{bmatrix} -1 & +1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_5^\top &= \begin{bmatrix} +1 & -1 & -1 \end{bmatrix}, \quad & \boldsymbol{w}_6^\top &= \begin{bmatrix} +1 & -1 & +1 \end{bmatrix}, \\
\boldsymbol{w}_7^\top &= \begin{bmatrix} +1 & +1 & -1 \end{bmatrix}, \quad & \boldsymbol{w}_8^\top &= \begin{bmatrix} +1 & +1 & +1 \end{bmatrix}.
\end{aligned}
$$

- $\mathcal{P}_{12} = \{(5, 8), (6, 7)\}$, $\mathcal{N}_{12} = \{(1, 4), (2, 3)\}$
- $\mathcal{P}_{13} = \{(3, 8), (4, 7)\}$, $\mathcal{N}_{13} = \{(1, 6), (2, 5)\}$
- $\mathcal{P}_{14} = \{(2, 8), (4, 6)\}$, $\mathcal{N}_{14} = \{(1, 7), (3, 5)\}$

Fiducial Generalized Pivotal Quantity (FGPQ)

- Let $\boldsymbol{Y}$ denote a random sample from a distribution that depends on a parameter vector $\boldsymbol{\xi}$
- Let $\boldsymbol{y}$ denote a realization of $\boldsymbol{Y}$
- Suppose that $\theta = f(\boldsymbol{\xi})$ is to be tested

Definition 2

A random quantity $R_\theta = R(\boldsymbol{Y}, \boldsymbol{y}, \boldsymbol{\xi})$ is called a fiducial generalized pivotal quantity (FGPQ) if

(A) The probability distribution of R_θ is free of all unknown parameters

(B) $R(\boldsymbol{y}, \boldsymbol{y}, \boldsymbol{\xi}) = \theta$ for every allowable $\boldsymbol{y}$

- A fiducial test variable T_θ can be defined as $T_\theta = R_\theta - \theta$ or $T_\theta = R_\theta / \theta$

Fiducial Generalized Pivotal Quantity (FGPQ)

- Let $R_{\delta_{st}}$ denote a random quantity given by

$$R_{\delta_{st}} = \frac{\prod_{(a,b)\in\mathcal{P}_{st}} \left(\frac{sse_a}{V_a}\frac{sse_b}{V_b}\right)^{\frac{1}{2p_{st}}}}{\prod_{(a,b)\in\mathcal{N}_{st}} \left(\frac{sse_a}{V_a}\frac{sse_b}{V_b}\right)^{\frac{1}{2n_{st}}}},$$

- The distribution of $R_{\delta_{st}}$ is free of all unknown parameters
- Since (a, b) is the quasi-foldover pair,

$$R_{\delta_{st}} = \delta_{st}$$

- $R_{\delta_{st}}$ is an FGPQ for δ_{st}

4.Identifying Active Dispersion Effects

- Test $H_0 : \delta_{st} = 1$ versus $H_1 : \delta_{st} \neq 1$
- Fiducial test variable

$$T_{\delta_{st}} = \frac{R_{\delta_{st}}}{\delta_{st}}$$

- The distribution of $T_{\delta_{st}}$ has no explicit form
- The Monte-Carlo method are used to calculate the p-value
- If p-value < 0.05, the addition order of components s and t may have a significant impact on the response variance

Simulation Studies

- $m = 6$
- $\mathcal{D} = \{12, 13, 14, 15\} \rightarrow 16$ groups
- Three template designs with 48, 64, and 80 runs
- Scenarios

	Active effects		df_g		
Scenario	Location effects	Dispersion effects	$n = 48$	$n = 64$	$n = 80$
1	$\{12\}$	$\{12\}$	2	3	4
2	$\{12\}$	$\{12, 13\}$	2	3	4
3	$\{12\}$	$\{12, 13, 14\}$	2	3	4
4	$\{56\}$	$\{12\}$	1	2	3
5	$\{56\}$	$\{12, 13\}$	1	2	3
6	$\{56\}$	$\{12, 13, 14\}$	1	2	3
7	$\{12, 56\}$	$\{12\}$	1	2	3
8	$\{12, 56\}$	$\{12, 13\}$	1	2	3
9	$\{12, 56\}$	$\{12, 13, 14\}$	1	2	3

- Simulation results are presented in Tables 3.2, 3.3, and 3.4

- The 64-run template design

		Dispersion effect				Average	
Scenario	δ	δ_{12}	δ_{13}	δ_{14}	δ_{15}	Size	Power
1	2	**0.296**	0.050	0.050	0.051	0.050	0.296
	4	**0.823**	0.050	0.054	0.048	0.051	0.823
	6	**0.959**	0.054	0.048	0.048	0.050	0.959
	8	**0.987**	0.050	0.048	0.048	0.049	0.987
2	2	**0.301**	**0.303**	0.046	0.052	0.049	0.302
	4	**0.820**	**0.818**	0.047	0.047	0.047	0.819
	6	**0.960**	**0.960**	0.050	0.050	0.050	0.960
	8	**0.991**	**0.988**	0.046	0.052	0.049	0.990
3	2	**0.288**	**0.294**	**0.293**	0.053	0.053	0.292
	4	**0.817**	**0.820**	**0.825**	0.051	0.051	0.821
	6	**0.955**	**0.959**	**0.960**	0.054	0.054	0.958
	8	**0.989**	**0.990**	**0.990**	0.047	0.047	0.990

- The proposed method can control the empirical sizes close to the nominal level 0.05

- The 64-run template design

		Dispersion effect				Average	
Scenario	δ	δ_{12}	δ_{13}	δ_{14}	δ_{15}	Size	Power
1	2	**0.296**	0.050	0.050	0.051	0.050	0.296
	4	**0.823**	0.050	0.054	0.048	0.051	0.823
	6	**0.959**	0.054	0.048	0.048	0.050	0.959
	8	**0.987**	0.050	0.048	0.048	0.049	0.987
2	2	**0.301**	**0.303**	0.046	0.052	0.049	0.302
	4	**0.820**	**0.818**	0.047	0.047	0.047	0.819
	6	**0.960**	**0.960**	0.050	0.050	0.050	0.960
	8	**0.991**	**0.988**	0.046	0.052	0.049	0.990
3	2	**0.288**	**0.294**	**0.293**	0.053	0.053	0.292
	4	**0.817**	**0.820**	**0.825**	0.051	0.051	0.821
	6	**0.955**	**0.959**	**0.960**	0.054	0.054	0.958
	8	**0.989**	**0.990**	**0.990**	0.047	0.047	0.990

- The empirical power increases when the effect size increases

- The 64-run template design

		Dispersion effect				Average	
Scenario	δ	δ_{12}	δ_{13}	δ_{14}	δ_{15}	Size	Power
1	2	**0.296**	0.050	0.050	0.051	0.050	0.296
	4	**0.823**	0.050	0.054	0.048	0.051	0.823
	6	**0.959**	0.054	0.048	0.048	0.050	0.959
	8	**0.987**	0.050	0.048	0.048	0.049	0.987
2	2	**0.301**	**0.303**	0.046	0.052	0.049	0.302
	4	**0.820**	**0.818**	0.047	0.047	0.047	0.819
	6	**0.960**	**0.960**	0.050	0.050	0.050	0.960
	8	**0.991**	**0.988**	0.046	0.052	0.049	0.990
3	2	**0.288**	**0.294**	**0.293**	0.053	0.053	0.292
	4	**0.817**	**0.820**	**0.825**	0.051	0.051	0.821
	6	**0.955**	**0.959**	**0.960**	0.054	0.054	0.958
	8	**0.989**	**0.990**	**0.990**	0.047	0.047	0.990

- The empirical powers are very close when there are several active dispersion effects

Scenario	Run size	δ	Dispersion effect δ_{12}	δ_{13}	δ_{14}	δ_{15}	Average Size	Power
2	48	2	**0.187**	**0.187**	0.047	0.054	0.050	0.187
		4	**0.577**	**0.580**	0.049	0.051	0.050	0.579
		6	**0.804**	**0.800**	0.053	0.050	0.052	0.802
		8	**0.898**	**0.901**	0.049	0.051	0.050	0.900
	64	2	**0.301**	**0.303**	0.046	0.052	0.049	0.302
		4	**0.820**	**0.818**	0.047	0.047	0.047	0.819
		6	**0.960**	**0.960**	0.050	0.050	0.050	0.960
		8	**0.991**	**0.988**	0.046	0.052	0.049	0.990
	80	2	**0.400**	**0.398**	0.052	0.050	0.051	0.399
		4	**0.932**	**0.932**	0.050	0.050	0.050	0.932
		6	**0.994**	**0.994**	0.049	0.052	0.050	0.994
		8	**0.999**	**0.999**	0.050	0.050	0.050	0.999

- The empirical power increases when the run size or the residual degrees of freedom are larger
- The proposed method appears to be feasible

Real Data Analysis

- Wang et al. (2020) conducted a 24-run four-drug combination experiment
- Whether or not different orders of four chemotherapeutics have a significant impact on human lymphoma cell growth
- The cell inhibition rate was measured

h	t_h	y_h	h	t_h	y_h
1	1234	27.31	13	1243	15.40
2	1342	37.30	14	1324	34.05
3	1423	24.42	15	1432	32.74
4	2143	23.30	16	2134	31.04
5	2314	29.29	17	2341	31.56
6	2431	26.01	18	2413	15.78
7	3124	35.98	19	3142	37.22
8	3241	39.48	20	3214	36.28
9	3412	36.78	21	3421	38.42
10	4132	33.16	22	4123	25.77
11	4213	25.81	23	4231	30.90
12	4321	31.17	24	4312	30.62

Real Data Analysis

- A standard stepwise regression is used to identify active location effects

$$\mathcal{L} = \{12, 23, 24, 34\}$$

- Location effects model

$$\begin{aligned}\hat{y}_h = 30 - 1.358 z_{h,12} - 3.301 z_{h,23} - 2.236 z_{h,24} + 3.796 z_{h,34} \\ + 1.224 z_{h,24} z_{h,34}.\end{aligned}$$

- With adjusted R-squared:0.859

Real Data Analysis

- To find potential dispersion effects
- Residual variance ratios

$$r_{ij} = \frac{\max\left[var(\boldsymbol{e}_{ij+}), var(\boldsymbol{e}_{ij-})\right]}{\min\left[var(\boldsymbol{e}_{ij+}), var(\boldsymbol{e}_{ij-})\right]}$$

where $\boldsymbol{e}_{ij+}$ and $\boldsymbol{e}_{ij-}$ denote the residual vectors corresponding to $z_{h,ij} = +1$ and $z_{h,ij} = -1$, respectively.

r_{12}	r_{13}	r_{14}	r_{23}	r_{24}	r_{34}
5.729	1.238	3.902	3.542	2.490	7.443

- $\mathcal{D} = \{12, 34\}$
- The observed data are divided into four groups

Real Data Analysis

- $\mathcal{I}_1 \longrightarrow SSE_1, \mathcal{I}_2 \longrightarrow SSE_2, \ldots, \mathcal{I}_4 \longrightarrow SSE_4$
- Calculate the fiducial test variable $T_{\delta_{12}}$ and $T_{\delta_{34}}$
- The p-value for $H_0 : \delta_{12} = 1$ is 0.037
- The p-value for $H_0 : \delta_{34} = 1$ is 0.122
- The addition order of components 1 and 2 may have a significant impact on the variance of the cell inhibition rate

Group-wise Exchange Algorithm

- Generate designs with a small run size is practical

$$R_{\delta_{st}} = \frac{\prod_{(a,b)\in\mathcal{P}_{st}} \left(\frac{sse_a}{V_a}\frac{sse_b}{V_b}\right)^{\frac{1}{2p_{st}}}}{\prod_{(a,b)\in\mathcal{N}_{st}} \left(\frac{sse_a}{V_a}\frac{sse_b}{V_b}\right)^{\frac{1}{2n_{st}}}}$$

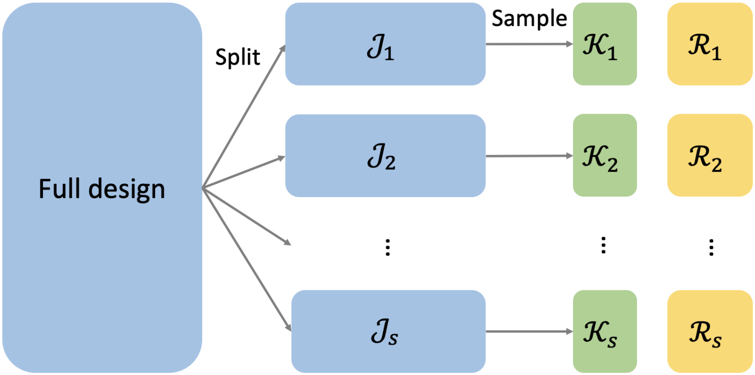
- The procedure is testable if $\mathcal{P}_{st} \neq \phi$ and $\mathcal{N}_{st} \neq \phi$

Corollary 1

Given a requirement set $\mathcal{D}$, an order-of-addition design is eligible if $\mathcal{I}_g \neq \phi$ for each $g = 1, 2, \ldots, s$.

Group-wise Exchange Algorithm

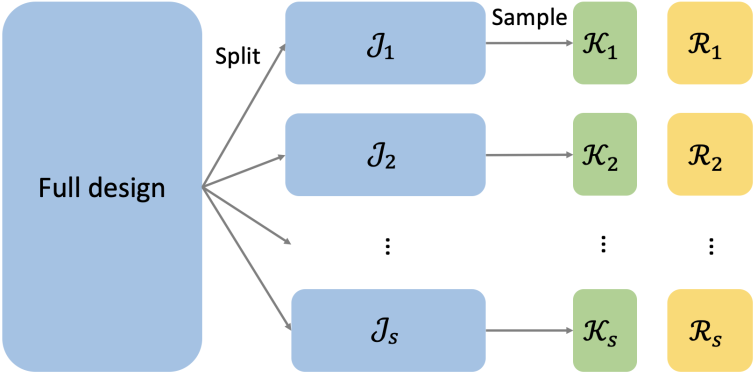
- Generate highly D-efficient eligible designs
- Inputs: m, n, and $\mathcal{D}$



1. Generate the full design

Group-wise Exchange Algorithm

- Generate highly D-efficient eligible designs
- Inputs: m, n, and $\mathcal{D}$



2. The full design is split into s groups according to $\mathcal{D}$

Group-wise Exchange Algorithm

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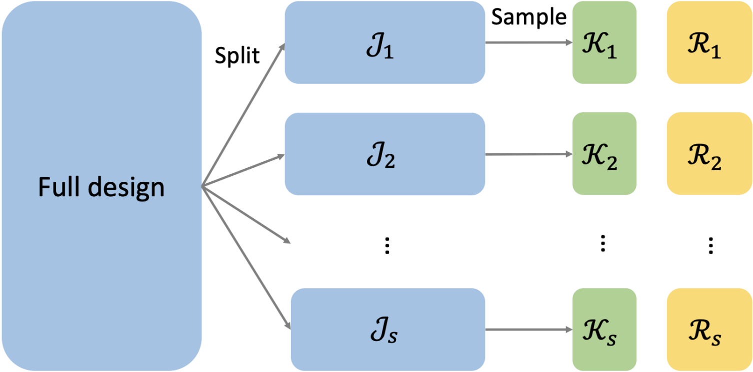

3. Sample $r = n/s$ indices from $\mathcal{J}_g$

Group-wise Exchange Algorithm

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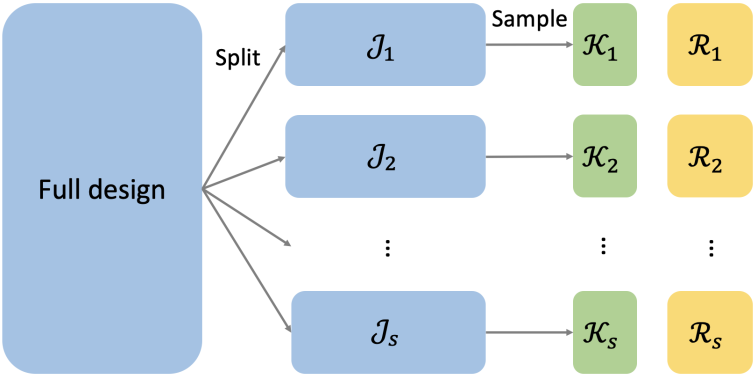
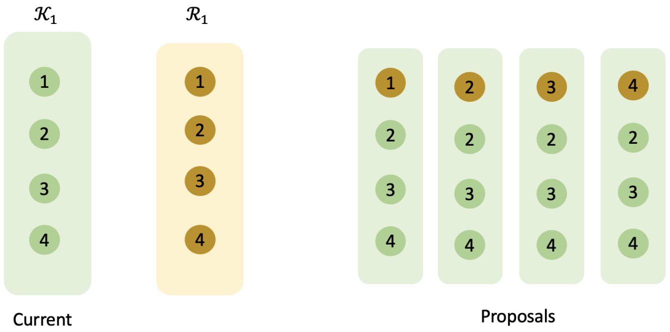
- Inputs: m, n, and $\mathcal{D}$



4. Combine $\mathcal{K}_1, \mathcal{K}_2, , \ldots, \mathcal{K}_s$ as the initial design and calculate the D-efficiency

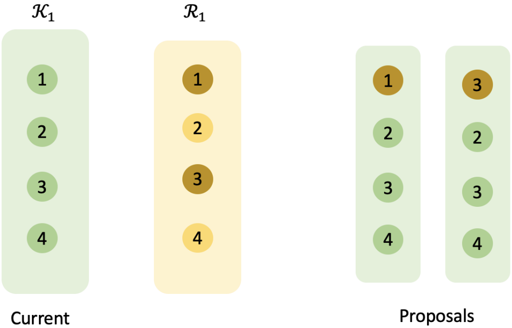
Group-wise Exchange Algorithm - Exhaustive



- The design is improved by considering all possible exchanges
- If the new proposal is more D-efficient, the current proposal is then replaced by the new proposal
- $\mathcal{R}_g$ is updated
- The procedure will be terminated if the current design cannot be improved

Group-wise Exchange Algorithm - Random

- When m gets large, it can become very time-consuming
- Adopt the random procedure
- Only consider $\pi \times |\mathcal{R}_g|$ elements, where $0 < \pi < 1$
- For example, $\pi = 0.5$



Performance of Group-wise Exchange Algorithm

- The relative D-efficiency of resulting designs with the computation time (s)

	Random				Exhaustive
	$\pi = 0.2$	$\pi = 0.4$	$\pi = 0.6$	$\pi = 0.8$	$\pi = 1.0$
$m = 7$	0.532 (1.062)	0.541 (1.797)	0.545 (2.407)	0.547 (2.892)	0.548 (3.327)
9	0.218 (128.588)	0.232 (233.413)	0.237 (306.819)	0.239 (375.421)	0.241 (411.345)

- Similar D-efficiencies with different π
- The computation times are very different
- When the design parameter m is large, the random search procedure is recommended for practical use

Summary

- The two-stage method is proposed
  1. Identify active location effects
  2. Identify active dispersion effects from the requirement set
- Based on simulation studies, the proposed method can maintain the empirical type I error rates
- A drug combination experiment is illustrated
- The group-wise exchange algorithm for constructing eligible designs

Thanks for your attention!