TWO TREATMENT CROSSOVER DESIGNS FOR ESTIMATING A VARIETY OF EFFECTS

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Abstract

This paper compares a variety of two treatment crossover designs under a uniform notation and covariance structure with respect to their ability to provide efficient estimators of contrasts among direct treatment effects when residual effects might be present. The designs are also compared on the basis of their ability to provide additional information on the nature of treatment effects such as estimating second order residual effects and direct by period and direct by first order residual effect interaction. Many of these designs are uniformly more efficient, with respect to estimating direct treatment effects, than either the conventional two period design or the completely randomized design with repeated measurements. Two efficient and effective four sequence designs are discussed in some detail.

KEY WORDS: Crossover designs; Repeated measurements designs; Direct treatment effects; Residual treatment effects.

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1. INTRODUCTION

The literature on two treatment crossover designs is underdeveloped. This situation is particularly awkward in view of the popularity enjoyed by an essentially simple design such as the two treatment two period crossover. Practitioners might be aware of the problems regarding estimation of residual treatment effects with this design (e.g., Grizzle 1965) and the current controversy surrounding the appropriateness of its use in clinical trials (Brown 1978); however, they often do not have the time to exhaustively search the literature and may not be aware of some three period (Brandt 1938; Lucas 1957) or four period (Quenouille 1953) alternatives.

This paper brings together these published designs and presents some new two treatment crossover designs in a unified setting. The designs are compared under a uniform notation and covariance structure with respect to their ability to provide efficient estimators of contrasts among direct treatment effects when residual effects might be present. The designs are also compared on the basis of their ability to provide additional information on the nature of the treatment effects such as estimating second order residual effects and direct by period and direct by first order residual effect interactions.

Following Hedayat and Afsarinejad (1975), we denote by RM(v,s,p) a repeated measurements (RM) design characterized by the administration of v treatments in s distinct sequences, or orderings, over p periods of time; i.e., each sampling unit receives p treatment applications. In this paper we will be considering two classes of RM designs; e.g., two treatment crossover designs and completely randomized designs with repeated measurements. We denote by CO(v,s,p) a crossover design consisting of v treatments administered in s distinct sequences over p periods of time. A completely randomized design with repeated measurements is characterized by having v = s and is denoted by CR(v,v,p). For p = 1 we have the familiar CR design.

Under our definition, a crossover design is any RM design having the property that at least one sampling unit receives at least two distinct treatments in at least two distinct periods. In CR(v,v,p) designs, sampling units receive p applications of the same treatment.

2. DEFINITIONS

RM designs differ from many of the conventional experimental designs in two major respects: the nature of the correlation structure of the errors and the nature of the treatment effects. In RM designs, treatments are applied in a serial sequence to a single sampling unit (e.g., a human, an animal, a plot of land, etc.). The repeated use of sampling units in this way introduces a variety of new concepts. These designs are used, for example, in growth and wear studies, clinical trials, educational and psychological studies, nutrition experiments, and long term agricultural experimentation. It was in this latter context that Cochran (1939) discussed the possibility that not only could treatments exert an effect in the period in which they were applied but also that the effects might carry over into succeeding periods; he called these the direct and residual treatment effects, respectively. Indeed, there can exist a variety of different treatment effects as described below.

2.1. Definitions

A direct treatment effect is the effect that a treatment has on the response of an experimental unit during the period of application. This is the type of effect commonly implied when analyzing designs such as the completely randomized, randomized complete block, latin square, etc. where the sampling unit receives only one treatment. A residual treatment effect is that effect of the treatment which lasts beyond the period of application. Residual effects are important in RM designs since they can bias the estimators of direct treatment effects. One must exercise care in choosing a design so as to enable residual effects to be

eliminated efficiently from comparisons of direct treatment effects.

There are several types of residual effects. First order residual effects are effects which last only one period beyond application. In a like manner, second, third, $\cdots$, $k^{\underline{th}}$ order residual effects last for two, three, and k periods, respectively, beyond the period of application. The magnitude of these residual effects is often a function of the length of the treatment period. Undiminished residual effects persist at a constant level after administration of treatment. When a uniform treatment is applied prior to experimentation, the sampling units may experience a common residual effect in period 1. These residual effects are called constant residual effects. In a similar fashion, first, second, $\cdots$, $k^{\underline{th}}$ order constant residual effects could uniformly affect the responses for all sampling units in the first, second, $\cdots$, $k^{\underline{th}}$ periods. These effects from a uniform pre-experimental treatment will be completely confounded with the period effects and therefore will not be estimable in models where period effects are present.

Continuing treatment effects last an indefinite time after administration of treatment. These effects may remain constant over time or they may gradually dampen out. Continuing treatment effects could be viewed as treatment cures in the context of clinical trials, for example. Once a patient is cured, further treatments will have no effect since a patient can only be cured once.

The arithmetic sum of the direct treatment effect and the first, second, $\cdots$, $k^{\underline{th}}$ order residual effects of that treatment was defined by Yates (1953) as the cumulative treatment effect. The effect so defined requires that there is no interaction between the various treatment effects. This effect has also been referred to as total treatment effect, or as permanent treatment effect by various authors; however, the term "cumulative" appears to be more descriptive of the exact nature of the mechanism of treatment effect. The limiting value of the cumulative effects was also defined by Yates (1953) as the stable value to which

the cumulative effect will tend if the experiment is carried on indefinitely. Given an exponential treatment response curve, the limiting value would be the asymptote.

The importance of these various treatment effects relative to one another is primarily a function of the purpose of the experiment. The effects of a given treatment on previous treatments are important in crop rotation experiments, e.g., where the object is to determine a succession of treatments over a series of years which give the best overall results. In contrast, the effects of previous treatments are usually of secondary importance in clinical trials where the prime interest is in measuring direct treatment effects and residual effects become unwanted effects to be eliminated from the direct treatment effects. Cumulative treatment effects are sometimes of more interest than either direct or residual effects separately. Lucas (1957) gives the example that, with dairy cows, fixed diets are given for longer periods of time than would be the case in crossover experiments, and he argued that the cumulative effects would offer better estimates of treatment effects than direct effects. Undiminished residual effects are important in the design of survey questionnaires which contain sensitive questions (e.g., questions relating to sex, income, drug use, etc.) since the cooperativeness of the respondent may tend to decrease after being asked such questions.

3. A LINEAR MODEL

We wish to initially adopt a model with sufficient generality to cover the broadest class of RM designs. For RM(v,s,p) a general linear model can be represented as

$$\begin{aligned} Y_{ijktru} = \eta_{ijktru}\{&\mu + \pi_i + \beta_j + \tau_t + \xi_{j(k)} + (1 - \delta_{1i})\rho_r \\ &+ \pi\pi_{ti} + (1 - \delta_{1i})\tau\rho_{tr} + (1 - \delta_{1i})\rho\pi_{ri} \\ &+ (1 - \delta_{1i})(1 - \delta_{2i})\rho_u^2 + \epsilon_{ijk}\} \end{aligned} \tag{3.1}$$

where

Y_{ijktru} = observed response for sampling unit k at period i in sequence j, $i = 1, \cdots, p$, $j = 1, \cdots, s$, $k = 1, \cdots, n_s$;

μ = effect due to an overall mean;

π_i = effect due to period i, $i = 1, \cdots, p$;

β_j = effect due to treatment sequence j, $j = 1, \cdots, s$;

$\xi_{j(k)}$ = random effect due to sampling unit k which is nested within sequence j, $j = 1, \cdots, s$, $k = 1, \cdots, n_s$;

τ_t = direct effect due to treatment t, $t = 1, \cdots, v$;

ρ_r = first order residual effect due to treatment r, $r = 1, \cdots, v$;

ρ_u^2 = second order residual effect due to treatment u, $u = 1, \cdots, v$;

δ_{1i} = the usual Kronecker delta such that $\delta_{1i} = \begin{cases} 1 & i = 1 \\ 0 & \text{otherwise} \end{cases}$;

$\tau\rho_{tr}$ = interaction effect due to $t^{\underline{th}}$ direct treatment effect and $r^{\underline{th}}$ first order residual effect;

$\tau\pi_{ti}$ = interaction effect due to $t^{\underline{th}}$ direct treatment effect and $i^{\underline{th}}$ period effect;

$\rho\pi_{ri}$ = interaction effect due to $r^{\underline{th}}$ first order residual effect and the $i^{\underline{th}}$ period effect;

ϵ_{ijk} = random effect associated with experimental error corresponding to the $i^{\underline{th}}$ serial observation on sampling unit k in sequence j.

Note that (3.1) is sufficiently general so that many models of particular interest will arise as special cases of (3.1). Several variations on (3.1) are given in Table 1.

INSERT TABLE 1 HERE

Understanding the nature of the covariance structure in RM designs is important in the context of constructing proper error terms for testing main effects and interactions and in the discussion of the efficiency of crossover designs relative to completely randomized designs. There appears to have been some confusion in the literature regarding the interplay between random effects due to the sampling units and correlation among repeated measurements on the same sampling unit (e.g., Grizzle 1965 and Winer 1971).

The random components in (3.1) are the effects due to the sampling units, the $\xi_{j(k)}$, and the effects due to error, the ϵ_{ijk}. We will initially assume that the sampling units represent a random sample from an infinite population and that they have zero mean and share a common variance. We view the $\xi_{j(k)}$ as representing an overall population mean level for the $jk^{\underline{th}}$ sampling unit while the ϵ_{ijk} are viewed as observations within these means. By virtue of this and as a direct consequence of the parameterization in (3.1), the $\xi_{j(k)}$ are not time dependent. The dependency across time is carried by the ϵ_{ijk}. The distributional assumptions we impose on the random effects in (3.1) are that the

$$\xi_{j(k)} \text{ are i.i.d. } N(0, \sigma_s^2)$$

and, independently,

$$\epsilon_{ijk} \text{ are i.d. } N(0, \sigma_e^2)$$

where

$$\text{cov}(\epsilon_{ijk}, \epsilon_{ijk}) = \rho_e \sigma_e^2 .$$

Thus in terms of the original observations we have that

$$\text{Cov}(Y_{ijktr}, Y_{i'j'k'tr}) = \begin{cases} \sigma_s^2 + \sigma_e^2 & i = i',\ j = j',\ k = k' \\ \sigma_s^2 + \rho_e \sigma_e^2 & i \neq i',\ j = j',\ k = k' \\ 0 & j \neq j',\ k \neq k' . \end{cases} \qquad (3.9)$$

On defining

$$\sigma^2 = \sigma_s^2 + \sigma_e^2$$

and

$$\rho = \frac{\sigma_s^2 + \rho_e \sigma_e^2}{\sigma^2}, \tag{3.10}$$

(3.9) can be rewritten as

$$\mathrm{Cov}(Y_{ijktr}, Y_{i'j'k'tr}) = \begin{cases} \sigma^2 & i = i',\ j = j',\ k = k' \\ \rho\sigma^2 & i \neq i',\ j = j',\ k = k' \\ 0 & j \neq j',\ k \neq k' . \end{cases}$$

It is further assumed that the $\xi_{j(k)}$ and ϵ_{ijktr} are uncorrelated with all of the fixed effects in (3.1).

Rather than defining ρ as in (3.10), other authors (e.g., Grizzle 1965 and Winer 1971) have adopted a parameterization as

$$\rho' = \sigma_s^2/\sigma^2 . \tag{3.11}$$

The covariance structure which gives rise to (3.11) carries the assumption that

$$\mathrm{Cov}(\epsilon_{ijk}, \epsilon_{i'jk}) = 0 .$$

A parameterization such as (3.11) arises naturally in mixed models, but it does not permit correlation among individual error terms within a sampling unit. In comparing the efficiency of CO designs relative to their CR counterparts, one should consider not only the magnitude of σ_s^2 relative to σ_e^2 but also the magnitude of ρ_e.

4. THE p-PERIOD COMPLETELY RANDOMIZED DESIGN UNDER A RESIDUAL EFFECTS MODEL

Since its introduction by Cochran, Autrey and Cannon (1941), the concept of residual effects seems to have remained within the domain of crossover designs

and rotation experiments. Here we investigate the properties of CR(2,2,p) under a model with first order residual effects. CR(2,2,p) is schematically shown in Table 2.

INSERT TABLE 2 HERE

On adopting (3.3) in Table 1, together with the error assumptions in (3.9), solution of the normal equations leads to

$$\widehat{\tau_1 - \tau_2} = \bar{y}_{11\cdot} - \bar{y}_{12\cdot} \tag{4.1}$$

and

$$\widehat{\rho_1 - \rho_2} = \frac{1}{p-1} \sum_{i=2}^{p} (\bar{y}_{i1\cdot} - \bar{y}_{i2\cdot}) - \bar{y}_{11\cdot} + \bar{y}_{12\cdot} \tag{4.2}$$

with

$$V(\widehat{\tau_A - \tau_B}) = 2N\sigma^2/n_1 n_2 \tag{4.3}$$

and

$$V(\widehat{\rho_A - \rho_B}) = pN\sigma_e^2(1 - \rho_e)/(p-1)n_1 n_2 \,. \tag{4.4}$$

We note that residual effects models are seldom used in designs such as CR(2,2,p). The complete confounding of direct treatment effects with first order residual effects for $p \geq 2$ restricts estimators of direct effects to functions of observations from the first period. Under residual effects models, CR(v,s,p) designs are inefficient since there is a substantial loss of information on direct treatment effects. The precision of estimators of direct effects does not depend upon the number of periods. However, the variance of the estimators of residual treatment effects does improve with increasing p, as is evident from (4.4).

5. TWO TREATMENT CROSSOVER DESIGNS

The two treatment two period crossover design is often the focus of criticism for its inability to provide efficient estimation of direct treatment effects when residual effects are present. Brown (1978) and unpublished reports from the Food and Drug Administration provide discussions of some of the problems with this design in more complex settings. In light of section 4, abandoning the crossover concept in favor of completely randomized designs does not appear to be an effective or efficient solution. Rather, one might consider extending the two treatment crossover designs for extra periods or using designs where observations are taken between periods of treatment application.

Fourteen two treatment crossover designs are schematically represented in Table 3. The schematics depict the placement of treatments with respect to the periods (rows) and sequences (columns) of the designs. As part of the randomization we note that sampling units are randomly assigned to the sequences of the design. CR(2,2,2) is included for the sake of completeness, but it should not be considered a viable design under the types of models we are considering here.

INSERT TABLE 3 HERE

Best linear unbiased estimators (b.l.u.e.'s) of estimable functions such as $\tau_A - \tau_B$ and $\rho_A - \rho_B$ are denoted by $\widehat{\tau_A - \tau_B}$ and $\widehat{\rho_A - \rho_B}$, respectively. The b.l.u.e.'s can be uniquely expressed as linear combinations of the period by sequence means. The forms of $\widehat{\tau_A - \tau_B}$ and $\widehat{\rho_A - \rho_B}$ for all designs are shown in Table 4 as coefficient matrices which give the weights of the period by sequence means. Estimation is carried out under model (3.3) in Table 1 for all designs, with the exception of CR(2,2,2) which requires a reduced model such as (3.6).

INSERT TABLE 4 HERE

The variances of $\widehat{\tau_A - \tau_B}$ and $\widehat{\rho_A - \rho_B}$ are computed using Table 4 and the covariance structure (3.9). These variances (multiplied by N/σ_e^2) are shown in Table 5, where $N = \sum_{i=1}^{s} n_{j\cdot}$. In computing the variances for each design, we have assumed that a total of N sampling units are available so that the variances are standardized for the total sample size and so are directly comparable between and within classes and subclasses. Also given in Table 5 are the ratios $V(\widehat{\rho_A - \rho_B})/V(\widehat{\tau_A - \tau_B})$ which show the precision of $\widehat{\rho_A - \rho_B}$ relative to $\widehat{\tau_A - \tau_B}$. The variances are ranked within classes and overall designs. CO(2,2,2) is unranked in view of the dependency of $V(\widehat{\tau_A - \tau_B})$ and $V(\widehat{\rho_A - \rho_B})$ on σ_s^2. Note that when $\sigma_s^2 \geq 2\sigma_e^2$ the variances of $\widehat{\tau_A - \tau_B}$ and $\widehat{\rho_A - \rho_B}$ from CO(2,2,2) will be the largest of any of the designs in Table 6.

INSERT TABLE 5 HERE

INSERT TABLE 6 HERE

Recall that CO(2,2,2) provides information on direct and residual effects only (see, for example, Grizzle 1965). The use of four sequences rather than two in a two period design, i.e., D2.2, permits estimation of residual effects without having to assume a reduced model such as (3.6). While the estimability problem is resolved, $V(\widehat{\tau_A - \tau_B}) = 8\sigma_e^2(1 - \rho_e)/N$ which is ranked thirteenth with respect to the alternative designs.

Using the rest period designs D3.1R or D3.2R might be reasonable alternatives to CO(2,2,2) in some situations. Because only two treatments are given over the three periods, use of these designs might be defendable on ethical grounds, but more information can be recovered if the individual sampling units can be treated more than twice.

With respect to minimizing $V(\widehat{\tau_A - \tau_B})$, D4.2 is clearly the design of choice. A possible undesirable feature of this design is that each sampling unit is exposed

to each treatment twice and thus its use might not be defendable on ethical or purely practical grounds. D3.2 and D3.4 are ranked second and third overall. With respect to D4.2, their efficiency for measuring direct effects is 0.67 and 0.65, respectively. With respect to D3.2, the efficiency of D3.4 is 0.97. With respect to CR designs the efficiencies of D3.2, D3.4 and D4.2 will be greater than one in general since $V(\widehat{\tau_A - \tau_B})$ from these designs does not depend on σ_s^2.

6. ESTIMABILITY PROPERTIES

Table 6 summarizes the estimability properties of the designs in Table 3 with respect to estimating a variety of treatment effects.

Within the two period class, D2.2 is an improvement over D2.1 since it allows estimation of first order residual effects and direct by period interaction under less restrictive models, but the b.l.u.e. of $\tau_A - \tau_B$ from D2.2 is not efficient with respect to other designs in Table 3.

The CO(2,2,3) designs, D3.1 - D3.3, allow partial recovery of treatment by period interaction but they do not permit estimation of second order residual effects or direct by first residual interaction. Thus their use might be restricted to situations where these effects might not be present. With respect to estimating a variety of treatment effects, the three period designs D3.4 - D3.7 and the four period design D4.2 allow recovery not only of first order residual effects but also second order residual effects and direct by period and direct by first order residual interaction.

7. PRECISION OF ESTIMATORS FOR DIRECT TREATMENT EFFECTS

One might question under what conditions CO(2,s,p) designs — in particular designs such as D2.1, D3.2, D3.4 and D4.2 — provide more precise estimators of $\tau_A - \tau_B$ than their completely randomized counterparts, e.g., CR(2,s,p). Grizzle (1965) addressed this question in a more restricted sense than we do here. For

reference sake, $V(\widehat{\tau_A - \tau_B})$ are shown for D2.1, D3.2, D3.4 and D4.2 and the comparable CR designs in Table 7. The variances were computed with and without residual effects present in the model, e.g., under (3.2) and (3.3). Note that for the model (3.2) crossover designs perform much better than CR unless $\rho_e < 0$ and σ_s^2 is some small fraction of σ_e^2. Under the extreme conditions $\rho_e \approx -1$ and $\sigma_s^2 \approx \sigma_e^2$,

$$V_{CR}(\widehat{\tau_A - \tau_B}) \leq V_{CO}(\widehat{\tau_A - \tau_B}) .$$

For $\rho_e \geq 0$, $V_{CO}(\widehat{\tau_A - \tau_B}) \leq V_{CR}(\widehat{\tau_A - \tau_B})$ with the variances being equal for D3.2 and D3.4 when $\rho_e = 0$ and $\sigma_s^2 = \sigma_e^2/24$.

In many applications, $\sigma_s^2 > \sigma_e^2$. When this is the case, CO designs perform uniformly better than CR.

For residual effects models like (3.8), CO(2,2,2) and CR(2,2,p) provide identical estimators and identical variances of these estimators of direct treatment effects. In models having residual effects, D3.2, D3.4 and D4.2 perform uniformly better than the CR designs regardless of the true value of ρ_e.

8. DISCUSSION

We have attempted to unify some concepts on two treatment crossover designs and provide some efficient alternatives to the two treatment two period design and completely randomized designs. It is hoped that rather than abandon the crossover concept, experimenters might be able to use designs such as D3.2, D3.4 or D4.2 or the p-period analogs in experimental situations when residual effects might be present. These designs avoid the estimability problems in CO(2,2,2) as noted by Grizzle (1965) and provide estimators of contrasts of direct treatment effects which are uniformly better than the CR designs in a variety of settings. If residual effects are of primary importance in an experiment, then the p-period CR design will be an optimal design for this purpose.

1. Some Models for Two Treatment RM Designs Adapted from (3.1)

Model No.	Parameters Supressed	$E(Y_{ijktru})$	Comment
(3.2)	$\underset{\sim}{\rho}$, $\underset{\sim}{\rho^2}$, $\underset{\sim\sim}{\pi\pi}$, $\underset{\sim\sim}{\tau\rho}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \pi_i + \beta_j + \tau_t$	Additive model. No residual effects.
(3.3)	$\underset{\sim}{\rho^2}$, $\underset{\sim\sim}{\pi\pi}$, $\underset{\sim\sim}{\tau\rho}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \pi_i + \beta_j + \tau_t + \rho_r$	Additive model with first order residual effects.
(3.4)	$\underset{\sim\sim}{\pi\pi}$, $\underset{\sim\sim}{\tau\rho}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \pi_i + \beta_j + \tau_t + \rho_r + \rho_u^2$	Additive model. First and second order residual effects.
(3.5)	$\underset{\sim}{\rho}$, $\underset{\sim}{\rho^2}$, $\underset{\sim\sim}{\tau\rho}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \pi_i + \beta_j + \tau_t + \pi\pi_{ti}$	No residual effect model with direct by period interaction. Used for $CO(v, v^2, p)$ by Balaam (1965).
(3.6)	$\underset{\sim}{\beta}$, $\underset{\sim}{\pi}$, $\underset{\sim}{\rho^2}$, $\underset{\sim\sim}{\pi\pi}$, $\underset{\sim\sim}{\tau\rho}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \tau_t + \rho_r$	Direct and residual effects only (e.g., Grizzle 1965).
(3.7)	$\underset{\sim}{\rho^2}$, $\underset{\sim\sim}{\pi\pi}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \pi_i + \beta_j + \tau_t + \rho_r + \tau\rho_{tr}$	
(3.8)	$\underset{\sim}{\beta}$, $\underset{\sim}{\rho^2}$, $\underset{\sim\sim}{\pi\pi}$, $\underset{\sim\sim}{\tau\rho}$, $\underset{\sim\sim}{\rho\pi}$	$\mu + \pi_i + \tau_t + \rho_r$	

2. A p-Period Completely Randomized Design for Two Treatments

Period	Treatment Group 1					Treatment Group 2				
	Sampling Units					Sampling Units				
	1	2	⋯		n_1	1	2	⋯		n_2
1	A	A	⋯		A	B	B	⋯		B
2	A	A	⋯		A	B	B	⋯		B
3	A	A	⋯		A	B	B	⋯		B
⋮	⋮	⋮	⋯		⋮	⋮	⋮	⋯		⋮
p	A	A	⋯		A	B	B	⋯		B

3. Schematic Representation of Some Two Treatment Crossover Designs

Class	Subclass CO(2,s,p)	Design No.	Design	Origin
2	CO(2,2,2)	D2.1	A B B A	
	CO(2,4,2)	D2.2	A B A B B A A B	Balaam (1965)
3	CO(2,2,3)	D3.1R	A B - - B A	
		D3.2R	A B B A - -	
		D3.1	A B A B B A	
		D3.2	A B B A B A	Lucas (1957)
		D3.3	A B B A A B	Brandt (1938)
	CO(2,4,3)	D3.4	A B A B A B B A B A B A	
		D3.5	A B A B A B B A B A A B	
		D3.6	A B A B B A B A B A A B	
	CO(2,6,3)	D3.7	A B A B A B A B B A B A B A B A A B	
4	CO(2,2,4)	D4.1R	A B - - B A - -	
		D4.1	A B B A A B B A	Brandt (1938)
	CO(2,4,4)	D4.2	A B A B A B B A B A B A B A A B	Quenouille (1953)

4. B.l.u.e.'s for $\tau_A - \tau_B$ and $\rho_A - \rho_B$ Expressed as Linear Combinations of Cell Means

Class	Subclass	Design No.	Design	Coefficient Matrix for $\hat{\tau}_A - \hat{\tau}_B$	Coefficient Matrix for $\hat{\rho}_A - \hat{\rho}_B$
2	CO(2,2,2)	D2.1	A B B A	$\begin{bmatrix} 1 & -1 \\ 0 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & -1 \\ 1 & -1 \end{bmatrix}$
	CO(2,4,2)	D2.2	A B A B B A A B	$\frac{1}{2}\begin{bmatrix} 1 & -1 & -1 & 1 \\ -1 & 1 & 1 & -1 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 & -1 & 1 \\ 0 & 0 & 1 & -1 \end{bmatrix}$
3	CO(2,2,3)	D3.1R	A B - - B A	$\frac{1}{2}\begin{bmatrix} 1 & -1 \\ 0 & 0 \\ -1 & 1 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \\ 1 & -1 \\ 0 & 0 \end{bmatrix}$
		D3.2R	A B B A - -	$\frac{1}{3}\begin{bmatrix} 2 & -2 \\ -1 & 1 \\ -1 & 1 \end{bmatrix}$	$\frac{1}{3}\begin{bmatrix} 1 & -1 \\ 1 & -1 \\ -2 & 2 \end{bmatrix}$
		D3.1	A B A B B A	$\frac{1}{2}\begin{bmatrix} 0 & 0 \\ 1 & -1 \\ -1 & 1 \end{bmatrix}$	$\begin{bmatrix} -1 & 1 \\ 1 & -1 \\ 0 & 0 \end{bmatrix}$
		D3.2	A B B A B A	$\frac{1}{4}\begin{bmatrix} 2 & -2 \\ -1 & 1 \\ -1 & 1 \end{bmatrix}$	$\frac{1}{2}\begin{bmatrix} 0 & 0 \\ 1 & -1 \\ -1 & 1 \end{bmatrix}$
		D3.3	A B B A A B	$\frac{1}{2}\begin{bmatrix} 2 & -2 \\ -1 & 1 \\ -1 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & -1 \\ 0 & 0 \\ -1 & 1 \end{bmatrix}$
	CO(2,4,3)	D3.4	A B A B A B B A B A B A	$\frac{1}{62}\begin{bmatrix} 6 & -6 & 16 & -16 \\ 9 & -9 & -5 & 5 \\ -15 & 15 & -11 & 11 \end{bmatrix}$	$\frac{1}{31}\begin{bmatrix} -7 & 7 & 2 & -2 \\ 5 & -5 & 11 & -11 \\ 2 & -2 & -13 & 13 \end{bmatrix}$
		D3.5	A B A B A B B A B A A B	$\frac{1}{8}\begin{bmatrix} 0 & 0 & 2 & -2 \\ 3 & -3 & -1 & 1 \\ -3 & 3 & -1 & 1 \end{bmatrix}$	$\frac{1}{4}\begin{bmatrix} -1 & 1 & 1 & -1 \\ 2 & -2 & 1 & -1 \\ -1 & 1 & -2 & 2 \end{bmatrix}$
		D3.6	A B A B B A B A B A A B	$\frac{1}{26}\begin{bmatrix} 8 & -8 & 4 & -4 \\ -1 & 1 & -5 & 5 \\ -7 & 7 & 1 & -1 \end{bmatrix}$	$\frac{1}{13}\begin{bmatrix} 2 & -2 & 1 & -1 \\ 3 & -3 & 2 & -2 \\ -5 & 5 & -3 & 3 \end{bmatrix}$
	CO(2,6,3)	D3.7	A B A B A B A B B A B A B A B A A B	$\frac{1}{68}\begin{bmatrix} 3 & -3 & 14 & -14 & 7 & -7 \\ 9 & -9 & -1 & 1 & -8 & 8 \\ -12 & 12 & -13 & 13 & 1 & -1 \end{bmatrix}$	$\frac{1}{34}\begin{bmatrix} -4 & 4 & 4 & -4 & 2 & -2 \\ 5 & -5 & 7 & -7 & 5 & -5 \\ -1 & 1 & -11 & 11 & -7 & 7 \end{bmatrix}$
4	CO(2,2,4)	D4.1R	A B - - B A - -	$\frac{1}{2}\begin{bmatrix} 1 & -1 \\ 0 & 0 \\ -1 & 1 \\ 0 & 0 \end{bmatrix}$	$\frac{1}{2}\begin{bmatrix} 0 & 0 \\ 1 & -1 \\ 0 & 0 \\ -1 & 1 \end{bmatrix}$
		D4.1	A B B A A B B A	$\frac{1}{4}\begin{bmatrix} 4 & -4 \\ -1 & 1 \\ -2 & 2 \\ 1 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & -1 \\ 0 & 0 \\ -1 & 1 \\ 0 & 0 \end{bmatrix}$
	CO(2,4,4)	D4.2	A B A B A B B A B A B A B A A B	$\frac{1}{8}\begin{bmatrix} 1 & -1 & 1 & -1 \\ 1 & -1 & -1 & 1 \\ -1 & 1 & -1 & 1 \\ -1 & 1 & 1 & -1 \end{bmatrix}$	$\frac{1}{22}\begin{bmatrix} -1 & 1 & 1 & -1 \\ 3 & -3 & 5 & -5 \\ 3 & -3 & -3 & 3 \\ -5 & 5 & -3 & 3 \end{bmatrix}$

5. Variances for $\widehat{\tau_A - \tau_B}$ and $\widehat{\rho_A - \rho_B}$ for Designs in Table 3 and for a Fixed Total Number of Observations N

Class	Subclass	Design No.	$V(\widehat{\tau_A - \tau_B})$ [1]	$V(\widehat{\rho_A - \rho_B})$ [1]	$\frac{V(\widehat{\rho_A - \rho_B})}{V(\widehat{\tau_A - \tau_B})}$	Class Rank [2]	Overall Rank [2]
2	CO(2,2,2)	D2.1	$4\left(\frac{\sigma_s^2}{\sigma_e^2} + 1\right)$	$8\left(\frac{2\sigma_s^2}{\sigma_e^2} + (1+\rho_e)\right)$			
	CO(2,4,2)	D2.2	$8(1 - \rho_e)$	$16(1 - \rho_e)$	2		13
3	CO(2,2,3)	D3.1R	$2(1 - \rho_e)$	$4\left(\frac{\sigma_s^2}{\sigma_e^2} + 1\right)$		5.5	7
		D3.2R	$\frac{8}{3}(1 - \rho_e)$	$\frac{8}{3}(1 - \rho_e)$	1	7	9
		D3.1	$2(1 - \rho_e)$	$8(1 - \rho_e)$	4	5.5	7
		D3.2	$3(1 - \rho_e)/2$	$2(1 - \rho_e)$	1.33	1	2
		D3.3	$6(1 - \rho_e)$	$8(1 - \rho_e)$	1.33	9	12
	CO(2,4,3)	D3.4	$48(1-\rho_e)/31$	$96(1-\rho_e)/31$	2	2	3
		D3.5	$3(1 - \rho_e)$	$6(1 - \rho_e)$	2	8	10
		D3.6	$24(1-\rho_e)/13$	$32(1-\rho_e)/13$	1.33	3.5	4.5
	CO(2,6,3)	D3.7	$63(1-\rho_e)/34$	$54(1-\rho_e)/17$	1.71	3.5	4.5
4	CO(2,2,4)	D4.1R	$2(1 - \rho_e)$	$2(1 - \rho_e)$	1	2	7
		D4.1	$11(1 - \rho_e)/2$	$8(1 - \rho_e)$	1.45	3	11
	CO(2,4,4)	D4.2	$(1 - \rho_e)$	$16(1-\rho_e)/11$	1.45	1	1

1/ Variances are multiplied by $\frac{N}{\sigma_e^2}$. All variances are computed using a fixed total sample size of N.

2/ Ranks are computed with respect to the precision of the estimators of $\tau_A - \tau_B$.

6. Estimability Properties of Some Two Treatment Crossover Designs Under a Variety of Models

Design	(Model) Parametric Function			
	(3.3) First order residual	(3.4) Second order residual	(3.5) Direct by period	(3.7) Direct by first order residual
D2.1	a	NE	NE	NE
D2.2	E	NE	E	NE
D3.1R	E	NE	NE	NE
D3.2R	E	NE	NE	NE
D3.1	E	NE	b	NE
D3.2	E	NE	b	NE
D3.3	E	NE	b	NE
D3.4	E	E	E	E
D3.5	E	E	E	E
D3.6	E	E	E	E
D3.7	E	E	E	E
D4.1R	E	NE	NE	NE
D4.1	E	E	c	NE
D4.2	E	E	E	E

E = estimable

NE = not estimable

a = requires reduced model, e.g. (3.6)

b = only 1 of the 2 linearly independent interaction contrasts are estimable.

c = only 2 of the 3 linearly independent interaction contrasts are estimable.

7. Variances for Estimators of Direct Treatment Effects for Some Two Treatment Crossover and Completely Randomized Designs

Design	No Residual Effects Present	Residual Effects Present
CO(2,2,2) [D2.1]	$2\sigma_e^2(1 - \rho_e)$	$4(\sigma_s^2 + \sigma_e^2)$
CR(2,2,2)	$4\sigma_s^2 + 2\sigma_e^2(1 + \rho_e)$	$4(\sigma_s^2 + \sigma_e^2)$
CO(2,2,3) [D3.2]	$3\sigma_e^2(1 - \rho_e)/2$	$3\sigma_e^2(1 - \rho_e)/2$
CR(2,2,3)	$\frac{2}{9}\{18\sigma_s^2 + 6\sigma_e^2 + 12\rho_e\sigma_e^2\}$	$4(\sigma_s^2 + \sigma_e^2)$
CO(2,2,3) [D3.4]	$3\sigma_e^2(1 - \rho_e)/2$	$48\sigma_e^2(1 - \rho_e)/31$
CR(2,2,4)	$4\sigma_s^2 + \sigma_e^2 + 3\rho_e\sigma_e^2$	$4(\sigma_s^2 + \sigma_e^2)$
CO(2,4,4) [D4.2]	$\sigma_e^2(1 - \rho_e)$	$\sigma_e^2(1 - \rho_e)$

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