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Brief Report

Higher Order C(t, p, s) Crossover Designs

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A crossover study is a repeated measures design in which each subject is randomly assigned to a sequence of treatments, including at least two treatments. The most damning characteristic of a crossover study is the potential of a carryover effect of one treatment to the next period. To solve the first-order crossover problem characteristic in the classic AB|BA design, the design must be extended. One alternative uses additional treatment sequences in two periods; a second option is to add a third period and repeat one of the treatments. Assuming a traditional model that specifies a first-order carryover effect, this study investigates the following alternative crossover trial designs: (1) two-treatment two-period four-sequence design (Balaam, 1968) design, (2) two treatments-three period-four sequence design (Ebbutt, 1984), and (3) three treatment-two period-six sequence design (Koch, 1983). Each design has attractive properties and, when properly applied, allows both treatment and carryover effects to be estimated.

Key words: Crossover design, Balaam's crossover design, Ebbutt's crossover design, Koch crossover design.

Introduction

The most damning characteristic of a crossover study is the potential for a carryover effect of one treatment to the next period. To manage this, researchers typically include washout periods in study designs. These washout periods are thought to be of sufficient length to negate any lingering effect of one treatment into the next period. In this article, and in most of the literature on crossover designs, the persistence of a carryover effect is assumed to (1) last for only a single period (a first-order carryover effect), and (2) a carryover effect is different for different treatments. If a carryover effect is suspected in any crossover trial, then a term for this effect must be included in the model and accounted for in subsequent analysis.

This study assumes a traditional model that specifies a first-order carryover effect and outlines three higher-order crossover designs: (1) a two-treatment two-period four-sequence design (Balaam, 1968), (2) a two treatments-three period-four sequence design (Ebbutt, 1984), and (3) a three treatment-two period-six sequence (Koch, 1983) design. Each design has appealing properties and - when properly applied - estimate both treatment and carryover effects.

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The Traditional Crossover Design Model with Continuous Data

The traditional crossover design with t-treatments, p-periods, and s-sequences, C(t, p, s), assumes that each treatment has a simple first-order carryover effect that does not interact with the direct effect of the treatment in the subsequent period, and that subject effects are either fixed or random. Though a variety of models are considered in the literature, virtually all work in crossover designs uses the same underlying statistical model. This model assumes the following for the response of patient y_{ij}: If y_{ij} denotes the observed response of subject j (j = 1, …, n) in period i (i = 1, …, p), then

$$y_{ij} = \mu + \pi_i + \tau_{d(i,j)} + \lambda_{d(i-1,j)} + \beta_j + \varepsilon_{ij}.$$

Where π_i is the effect of period i, $\tau_{d(i,j)}$ is the direct effect of treatment D, $\lambda_{d(i-1,j)}$ is the simple first-order carryover effect of treatment D, d(i, j) is the treatment allocated to patient j in period i, and $\lambda_{d(0,j)} = 0$ for all j. It is assumed that all effects are fixed effects. β_j is the effect of patient j and ε_{ij} is the error term. The random subject effect, β_j, and the experimental error, ε_{ij}, are assumed to be mutually independently distributed as N $(0, \sigma^2_\beta)$ and N $(0, \sigma^2_\varepsilon)$.

The primary purpose of a crossover design comparing treatments A and B is to estimate the treatment contrast $\tau_A - \tau_B$. The period effects (π_1 and π_2), the first order carryover effects (λ_A and λ_B) and μ are typically regarded as nuisance parameters that are desirable to eliminate from any estimate. To solve the first-order crossover problem in the two-treatment two-period crossover design, one possible solution is to extend the design to four sequences. Balaam's C(2, 2, 4) design (Balaam, 1968), AA|AB|BA|BB, is generally accepted as optimal for estimating treatment effects and is also more efficient than the classic C(2, 2, 2) design (Laska, Meisner & Kushner, 1983). If the carryover effect is absent, this design is inefficient because many subjects likely will not contribute any information to the estimate of treatment differences in the two sequences AA and BB. Using Balaam's design, unbiased estimates of the treatment differences and carryover effects are easily derived (see Table 1).

The second design strategy is to extend the classic design by adding a third period and repeating one of the two treatments. The treatment sequences will ensure that the first two trial periods constitute a conventional two-period crossover trial if the third treatment period leads to excessive subject drop-outs. Ebbutt's efficient C(2, 3, 4) design, the ABB| BAA|ABA|BAB (Ebbutt, 1984) illustrates this second strategy. This design, with equal number of subjects per sequence, is able to estimate all parameters in the traditional model and provide an unbiased estimate of the treatment contrast (Ebbutt, 1984; Heydat & Stufken, 2003; Liang & Carriere, 2010) (see Table 2). The expected values for each of the sequences are: $E[c_1] = E[(2y_{11} - y_{21} - y_{31})]$, $E[c_2] = E[(2y_{21} - y_{22} - y_{32})]$, $E[c_3] = E[(2y_{31} - y_{32} - y_{33})]$, and $E[c_4] = E[(2y_{41} - y_{42} - y_{43})]$. The linear contrast of $\frac{1}{2}(c_1 - c_2 + c_3 - c_4)$ forms an unbiased estimate of $\tau_A - \tau_B$. In testing for carryover effect, let c_i, i = 5, …, $8 = E[y_{1i} + y_{2i} - y_{3i}]$. The contrast $c_5 - c_6 + c_7 - c_8$ forms an unbiased estimate of $\lambda_A - \lambda_B$.

Koch's crossover design comparing two treatments A and B to a placebo P, uses six sequences AB, BA, AP, BP, PA, and PB (see Table 3). These six sequences enable the estimation of period effects, treatment effects and carryover effects from within-subject information. The four hypotheses of interest are: (1) $\tau_A - \tau_B$, (2) $\tau_A - \tau_P$, (3) $\tau_{\mathbf{B}} - \tau_P$, and (4) $\lambda_B - \lambda_A$. The linear contrast $(c_5 - c_6)$ forms an unbiased estimate of $\tau_A - \tau_B$; the linear contrast $(c_4 - c_2)$ forms an unbiased estimate of $\tau_A - \tau_P$; the linear contrast $(c_1 - c_3)$ forms an unbiased estimate of $\tau_{\mathbf{B}} - \tau_P$; and the linear contrast $(c_2 - c_1)$ forms an unbiased estimate of $\lambda_B - \lambda_A$.

Koch's C(3, 2, 6) design has six sequences, AB, BA, AC, CA, BC and CB (see Table 4). In this design, the hypotheses of interest are: (1) $\tau_A - \tau_B$, (2) $\tau_A - \tau_C$, (3) $\tau_{\mathbf{B}} - \tau_C$, (4) $\lambda_A - \lambda_B$, (5) $\lambda_A - \lambda_C$, and (6) $\lambda_B - \lambda_C$. The linear contrast $(c_1 - c_3)$ forms an unbiased estimate of $\tau_B - \tau_C$; the linear contrast $(c_2 - c_5)$ forms an unbiased estimate of $\tau_A - \tau_C$; and the linear contrast $(c_4 - c_6)$ forms an unbiased estimate of $\tau_{\mathbf{B}} - \tau_A$. For the three carryover hypotheses the linear contrast $(c_{1'} - c_{2'})$ forms an unbiased estimate of $\lambda_A - \lambda_B$; the linear contrast $(c_{3'} - c_{4'})$ forms an unbiased estimate of $\lambda_A - \lambda_C$; and the linear contrast $(c_{5'} - c_{6'})$ forms an unbiased estimate of $\lambda_B - \lambda_C$.

Conclusion

Optimal crossover designs are statistically efficient and require fewer subjects for the same number of observations than do non-crossover designs. Because variability is typically less within a subject than between different subjects, there is a corresponding increase in the precision of observations. The result: fewer subjects are required to detect a treatment difference. For example, if $N_{parallel}$ is the total number of subjects required for a two-way parallel trial to detect a treatment effect (δ) with 5% significance and 80% power, the total number of subjects $N_{crossover}$ required for a 2 x 2 crossover trial to detect the same effect is approximately

$N_{crossover} = (1 - r)N_{parallel}/2$, where r is a correlation coefficient among the repeated measurements of the primary endpoint.

The major concern - and subject of countless discussions - in a crossover study is the presence of a carryover effect. The standard way to avoid the carryover effect is to include a rest period between successive periods, hoping that the carryover effect will wash out. The inclusion of a rest period between each pair of successive periods increases the total duration of the experiment and there is no guarantee that any carryover effect will be eliminated.

To address the potential of first-order carryover effects, the classic AB|BA crossover design could easily be extended to one of the designs outlined herein. In effect, either the added sequence(s) or added treatment period permits direct estimates of treatment effect and examination of any carryover effects.

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Table 1: Balaam's Design (AB|BA|AA|BB)

AB|BA Design	Period 1 (k = 1)	Period 2 (k = 2)
Sequence AB (i = 1)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$
Sequence BA (i = 2)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$
Sequence AA (i = 3)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_A + \lambda_A$
Sequence BB (i = 4)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_B + \lambda_B$

Table 1 Notes:

Sequence AB (i = 1): $E(y_{AB,1}) = \mu_{AB,1} = \mu + \pi_1 + \tau_A$, $E(y_{AB,2}) = \mu_{AB,2} = \mu + \pi_2 + \tau_B + \lambda_A$
Sequence BA (i = 2): $E(y_{BA,1}) = \mu_{BA,1} = \mu + \pi_1 + \tau_B$, $E(y_{AB,2}) = \mu_{BA,2} = \mu + \pi_2 + \tau_A + \lambda_B$
Sequence AA (i = 3): $E(y_{BA,1}) = \mu_{AA,1} = \mu + \pi_1 + \tau_A$, $E(y_{AB,2}) = \mu_{BA,2} = \mu + \pi_2 + \tau_A + \lambda_A$
Sequence BB (i = 4): $E(y_{BA,1}) = \mu_{BA,1} = \mu + \pi_1 + \tau_B$, $E(y_{AB,2}) = \mu_{BA,2} = \mu + \pi_2 + \tau_B + \lambda_B$

In sequence AB, contrast c_1 has expected value: $E[c_1] = E[y_{11} - y_{21}] = (\pi_1 - \pi_2) + (\tau_A - \tau_B) - \lambda_A$
In sequence BA, contrast c_2 has expected value: $E[c_2] = E[y_{21} - y_{22}] = (\pi_1 - \pi_2) - (\tau_A - \tau_B) - \lambda_B$
In sequence AA, contrast c_3 has expected value: $E[c_3] = E[y_{31} - y_{32}] = (\pi_1 - \pi_2) - \lambda_A$
In sequence BB, contrast c_4 has expected value: $E[c_4] = E[y_{41} - y_{42}] = (\pi_1 - \pi_2) - \lambda_B$

In sequence AB, contrast c_5 has expected value: $E[c_5] = E[y_{11} + y_{21}] = 2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_B) + \lambda_A$
In sequence BA, contrast c_6 has expected value: $E[c_6] = E[y_{21} + y_{22}] = 2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_B) + \lambda_B$

Table 2: Ebbutt AAB|BAA|ABA|BAB Design

AB|BA Design	Period 1 (k = 1)	Period 2 (k = 2)	Period 3 (k = 3)
ABB (i = 1)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$
BAA (i=2)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$
ABA (i = 3)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$
BAB (i = 4)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$

Table 2 Notes:

ABB (i = 1): $E(y_{ABB,1}) = \mu + \pi_1 + \tau_A$, $E(y_{ABB,2}) = \mu + \pi_2 + \tau_A + \lambda_B$, $E(y_{ABB,3}) = \mu + \pi_3 + \tau_A + \lambda_B$
BAA (i = 2): $E(y_{BAB,1}) = \mu + \pi_1 + \tau_B$, $E(y_{BAB,2}) = \mu + \pi_2 + \tau_A + \lambda_B$, $E(y_{BAB,2}) = \mu + \pi_3 + \tau_A + \lambda_A$
ABA (i = 3): $E(y_{ABA,1}) = \mu + \pi_1 + \tau_A$, $E(y_{ABA,2}) = \mu + \pi_2 + \tau_A + \lambda_A$, $E(y_{ABA,3}) = \mu + \pi_3 + \tau_A + \lambda_B$
BAB (i = 4): $E(y_{AAB,1}) = \mu + \pi_1 + \tau_B$, $E(y_{AAB,2}) = \mu + \pi_2 + \tau_A + \lambda_B$, $E(y_{AAB,3}) = \mu + \pi_3 + \tau_B + \lambda_A$

In sequence ABB, the expected value $E[c_1]=E[(2y_{11} - y_{21} - y_{31})]=\{(2\pi_1 - \pi_2 - \pi_3) + 2(\tau_A - \tau_B) - \lambda_A - \lambda_B\}$
In sequence BAA, the expected value $E[c_2]=E[(2y_{21} - y_{22} - y_{32})]=\{(2\pi_1 - \pi_2 - \pi_3) + 2(\tau_A - \tau_B) - \lambda_A - \lambda_B\}$
In sequence ABA, the expected value $E[c_3]=E[(2y_{31} - y_{32} - y_{33})]=\{(2\pi_1 - \pi_2 - \pi_3) + (\tau_A - \tau_B) - \lambda_A - \lambda_B\}$
In sequence BAB, the expected value $E[c_4]=E[(2y_{41} - y_{42} - y_{43})]=\{(2\pi_1 - \pi_2 - \pi_3) - (\tau_A - \tau_B) - \lambda_A - \lambda_B\}$

In sequence ABB, the expected value $E[c_5]=E[(y_{11} + y_{21} - y_{31})]=\{2\mu + (\pi_1 + \pi_2 - \pi_3) + \tau_A + (\lambda_A - \lambda_B)\}$
In sequence BAA, the expected value $E[c_6]=E[(y_{21} + y_{22} - y_{32})]=\{2\mu + (\pi_1 + \pi_2 - \pi_3) + \tau_B - (\lambda_A - \lambda_B)\}$
In sequence ABA, the expected value $E[c_7]=E[(y_{31} + y_{32} - y_{33})]=\{2\mu + (\pi_1 + \pi_2 - \pi_3) + \tau_B + (\lambda_A - \lambda_B)\}$
In sequence BAB, the expected value $E[c_8]=E[(y_{41} + y_{42} - y_{43})]=\{2\mu + (\pi_1 + \pi_2 - \pi_3) + \tau_A - (\lambda_A - \lambda_B)\}$

Table 3: Koch Design (Treatments A, B and Placebo P)

Sequence	Period 1 (k = 1)	Period 2 (k = 2)
AB (i = 1)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$
BA (i = 2)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$
AP (i = 3)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_P + \lambda_A$
BP (i = 4)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_P + \lambda_B$
PA (i = 5)	$\mu + \pi_1 + \tau_P$	$\mu + \pi_2 + \tau_A + \lambda_P$
PB (i = 6)	$\mu + \pi_1 + \tau_P$	$\mu + \pi_2 + \tau_B + \lambda_P$

Table 3 Notes:

Sequence AB (i = 1): $E(y_{AB,1}) = \mu + \pi_1 + \tau_A$, $E(y_{AB,1}) = \mu + \pi_2 + \tau_B + \lambda_A$
Sequence BA (i = 2): $E(y_{AB,1}) = \mu + \pi_1 + \tau_B$, $E(y_{AB,1}) = \mu + \pi_2 + \tau_A + \lambda_B$
Sequence AP (i = 3): $E(y_{AB,1}) = \mu + \pi_1 + \tau_A$, $E(y_{AB,1}) = \mu + \pi_2 + \tau_P + \lambda_A$
Sequence BP (i = 4): $E(y_{AB,1}) = \mu + \pi_1 + \tau_B$, $E(y_{AB,1}) = \mu + \pi_2 + \tau_P + \lambda_B$
Sequence PA (i = 5): $E(y_{AB,1}) = \mu + \pi_1 + \tau_P$, $E(y_{AB,1}) = \mu + \pi_2 + \tau_A + \lambda_P$
Sequence PB (i = 6): $E(y_{AB,1}) = \mu + \pi_1 + \tau_P$, $E(y_{AB,1}) = \mu + \pi_2 + \tau_B + \lambda_P$

In sequence AB, contrast c_1 has expected value: $E[c_1] = E[(y_{11} - y_{12})] = (\pi_1 - \pi_2) + (\tau_A - \tau_B) - \lambda_A$
In sequence BA, contrast c_2 has expected value: $E[c_2] = E[(y_{21} - y_{22})] = (\pi_1 - \pi_2) - (\tau_A - \tau_B) - \lambda_B$
In sequence AP, contrast c_3 has expected value: $E[c_3] = E[(y_{31} - y_{32})] = (\pi_1 - \pi_2) + (\tau_A - \tau_P) - \lambda_A$
In sequence BP, contrast c_4 has expected value: $E[c_4] = E[(y_{41} - y_{42})] = (\pi_1 - \pi_2) + (\tau_B - \tau_P) - \lambda_B$
In sequence PA, contrast c_4 has expected value: $E[c_5] = E[(y_{51} - y_{52})] = (\pi_1 - \pi_2) - (\tau_A - \tau_P) - \lambda_P$
In sequence PB, contrast c_6 has expected value: $E[c_6] = E[(y_{61} - y_{62})] = (\pi_1 - \pi_2) - (\tau_B - \tau_P) - \lambda_P$

Table 4: Koch Design (Three Treatments, Two Periods)

Sequence	Period 1 (k = 1)	Period 2 (k = 2)
AB (i = 1)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$
BA (i = 2)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$
AC (i = 3)	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_C + \lambda_A$
CA (i = 4)	$\mu + \pi_1 + \tau_C$	$\mu + \pi_2 + \tau_A + \lambda_C$
BC (i = 5)	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_C + \lambda_B$
CB (i = 6)	$\mu + \pi_1 + \tau_C$	$\mu + \pi_2 + \tau_B + \lambda_C$

Table 4 Notes:

Sequence AB (i = 1): $E(y_{AB,1}) = \mu + \pi_1 + \tau_A$, $E(y_{AB,2}) = \mu + \pi_2 + \tau_B + \lambda_A$
Sequence BA (i = 2): $E(y_{AB,1}) = \mu + \pi_1 + \tau_B$, $E(y_{AB,2}) = \mu + \pi_2 + \tau_A + \lambda_B$
Sequence AC (i = 3): $E(y_{AB,1}) = \mu + \pi_1 + \tau_A$, $E(y_{AB,2}) = \mu + \pi_2 + \tau_C + \lambda_A$
Sequence CA (i = 4): $E(y_{AB,1}) = \mu + \pi_1 + \tau_C$, $E(y_{AB,2}) = \mu + \pi_2 + \tau_A + \lambda_C$
Sequence BC (i = 5): $E(y_{AB,1}) = \mu + \pi_1 + \tau_B$, $E(y_{AB,2}) = \mu + \pi_2 + \tau_C + \lambda_B$
Sequence CB (i = 6): $E(y_{AB,1}) = \mu + \pi_1 + \tau_C$, $E(y_{AB,2}) = \mu + \pi_2 + \tau_B + \lambda_C$

In sequence AB, contrast c_1 has expected value: $E[c_1] = E[(y_{11} - y_{12})] = (\pi_1 - \pi_2) + (\tau_A - \tau_B) - \lambda_A$
In sequence BA, contrast c_2 has expected value: $E[c_2] = E[(y_{21} - y_{21})] = (\pi_1 - \pi_2) - (\tau_A - \tau_B) - \lambda_B$
In sequence AC, contrast c_3 has expected value: $E[c_3] = E[(y_{31} - y_{21})] = (\pi_1 - \pi_2) + (\tau_A - \tau_C) - \lambda_A$
In sequence CA, contrast c_4 has expected value: $E[c_4] = E[(y_{41} - y_{21})] = (\pi_1 - \pi_2) - (\tau_A - \tau_C) - \lambda_C$
In sequence BC, contrast c_5 has expected value: $E[c_5] = E[(y_{51} - y_{21})] = (\pi_1 - \pi_2) + (\tau_B - \tau_C) - \lambda_B$
In sequence CB, contrast c_6 has expected value: $E[c_6] = E[(y_{61} - y_{21})] = (\pi_1 - \pi_2) - (\tau_B - \tau_C) - \lambda_C$

In sequence AB, contrast $c_{1'}$ has expected value: $E[c_{1'}] = E[(y_{11} + y_{12})] = 2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_B) + \lambda_A$
In sequence BA, contrast $c_{2'}$ has expected value: $E[c_{2'}] = E[(y_{21} + y_{22})] = 2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_B) + \lambda_B$
In sequence AC, contrast $c_{3'}$ has expected value: $E[c_{3'}] = E[(y_{31} + y_{32})] = 2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_C) + \lambda_A$
In sequence CA, contrast $c_{4'}$ has expected value: $E[c_{4'}] = E[(y_{41} + y_{42})] = 2\mu + (\pi_1 + \pi_2) + (\tau_A + \tau_C) + \lambda_C$
In sequence BC, contrast $c_{5'}$ has expected value: $E[c_{5'}] = E[(y_{51} + y_{52})] = 2\mu + (\pi_1 + \pi_2) + (\tau_B + \tau_C) + \lambda_B$
In sequence CB, contrast $c_{6'}$ has expected value: $E[c_{6'}] = E[(y_{61} + y_{62})] = 2\mu + (\pi_1 + \pi_2) + (\tau_B + \tau_C) + \lambda_C$