Analysis of Variance and Design of Experiments-II

MODULE VII

LECTURE - 32

CROSS-OVER DESIGNS

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Parametrization number 1(a)

If the test for no carry-out effect does not reject $H_0 : \lambda = 0$ against $H_1 : \lambda \neq 0$ using the test statistic $F_{1,df} = \hat{\lambda}_d^2 / Var(\hat{\lambda}_d)$, then our model can be reduced to the following

$$\tilde{X}_1 \tilde{\beta}_1 = \begin{pmatrix} 1 & 1 & 1 \\ 1 & -1 & -1 \\ 1 & 1 & -1 \\ 1 & -1 & 1 \end{pmatrix} \begin{pmatrix} \mu \\ \pi \\ \tau \end{pmatrix}$$

and we get the same estimators $\hat{\mu}$ and $\hat{\pi}$ as earlier given by

$$\hat{\mu} = \bar{y}_{ooo}$$

$$\hat{\pi} = \frac{\bar{y}_{11o} - \bar{y}_{21o}}{2} = \frac{\bar{c}_{10} - \bar{c}_{20}}{4} = \frac{\hat{\pi}_d}{2}.$$

The estimator $\hat{\tau}$ is now based on the data of both the periods.

$$\hat{\tau} = \frac{(\bar{y}_{11o} - \bar{y}_{12o} - \bar{y}_{21o} + \bar{y}_{22o})}{4}$$

$$= \frac{(\bar{d}_{1o} - \bar{d}_{2o})}{4}$$

$$= \frac{\hat{\tau}_d}{2}.$$

The difference between the results of parameterization numbers 1 and 1(a) is that the dependency in estimating the treatment effect τ and carry-over effect λ is explained. Other estimates $\hat{\pi}, \hat{\tau}$ and $\hat{\lambda}$ remain the same except for a factor.

Parametrization number 2

In the first parametrization, the interaction *treatment* x *period* was aliased with the carry-over effect λ. We now want to parametrize this interaction directly. Dropping the sequence effect, the model is

$$E(y_{ijk}) = \mu_{ij} = \mu + \pi_j + \tau_t + (\tau\pi)_{tj}.$$

The codings of the interaction effects are just the products of the codings involved in main effects. Therefore, we get the reduced model as

$$
\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = X_2\beta_2 = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & -1 & -1 & 1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \pi \\ \tau \\ (\pi\tau) \end{pmatrix}.
$$

Since the column vectors are orthogonal, we have $| X_2'X_2 | = 4I_4$ and, therefore, the parameter estimations are independent. The estimators are

$$
\hat{\beta}_2 = \begin{pmatrix} \hat{\mu} \\ \hat{\pi} \\ \hat{\tau} \\ \widehat{\pi\tau} \end{pmatrix} = \begin{pmatrix} \overline{y}_{ooo} \\ \hat{\pi}_d / 2 \\ (\overline{y}_{11o} - \overline{y}_{12o} - \overline{y}_{21o} + \overline{y}_{22o})/4 \\ (y_{11o} + \overline{y}_{12o} - \overline{y}_{21o} - \overline{y}_{22o})/4 \end{pmatrix}.
$$

Note that $\hat{\mu} = \hat{y}_{ooo}$ and $\hat{\pi} = \dfrac{\hat{\pi}_d}{2}$ are the same as in the first parameterization.

The estimator of $\hat{\tau}$ in this case coincides with the estimator

$$\hat{\tau} = \frac{\overline{d}_{1o} - \overline{d}_{2o}}{4} = \frac{\hat{\tau}_d}{2}$$

in the reduced model.

The estimator $\widehat{(\pi\tau)}$ is now

$$\widehat{\pi\tau} = \frac{(\overline{y}_{1oo} - \overline{y}_{2oo})}{2} = \frac{\hat{\lambda}_d}{4} = \frac{\hat{\lambda}}{2},$$

and coincides with the estimator of the carry-over effect except for a factor of 1/2 as

$$\hat{\lambda} = \overline{y}_{1oo} - \overline{y}_{2oo} = \frac{\hat{\lambda}_d}{2}$$

in the model
$$X_1\beta_1 = \begin{pmatrix} 1 & 1 & 1 & 0 \\ 1 & -1 & -1 & 1 \\ 1 & 1 & -1 & 0 \\ 1 & -1 & 1 & -1 \end{pmatrix}\begin{pmatrix} \mu \\ \pi \\ \tau \\ \lambda \end{pmatrix}$$

So it is obvious that there is an intrinsic aliasing between the two parameters λ and $(\pi\tau)$.

Parametrization number 3

Suppose that a carry-out effect λ or, alternatively, an interaction effect $(\pi\tau)$ may be excluded from analysis. Then the

model now contains only the main effects. Now we introduce the sequence effect γ as an additional main effect.

With $\gamma_2 = -\gamma_1 = \gamma,$ we get

$$
\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = X_3\beta_3 = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & 1 & -1 \\ 1 & -1 & -1 & 1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma \\ \pi \\ \tau \end{pmatrix},
$$

$$
(X_3'X_3) = 4I_4,
$$

$$
\hat{\beta}_3 = \begin{pmatrix} \hat{\mu} \\ \hat{\gamma} \\ \hat{\pi} \\ \hat{\tau} \end{pmatrix} = \frac{1}{4}X_3' \begin{pmatrix} \overline{y}_{11o} \\ \overline{y}_{12o} \\ \overline{y}_{21o} \\ \overline{y}_{22o} \end{pmatrix}
$$

$$
= \begin{pmatrix} \overline{y}_{ooo} \\ (\overline{y}_{11o} + \overline{y}_{12o} + \overline{y}_{21o} - \overline{y}_{22o})/4 \\ (\overline{y}_{11o} - \overline{y}_{12o} + \overline{y}_{21o} - \overline{y}_{22o})/4 \\ (\overline{y}_{11o} - \overline{y}_{12o} - \overline{y}_{21o} + \overline{y}_{22o})/4 \end{pmatrix}
$$

$$
= \begin{pmatrix} \overline{y}_{ooo} \\ (\overline{y}_{1oo} - \overline{y}_{2oo})/2 \\ (\overline{y}_{o1o} - \overline{y}_{o2o})/2 \\ \hat{\tau}_d/2 \end{pmatrix}.
$$

The sequence effect γ is estimated using the contrast in the total response of both group (AB) and (BA) and

$$\hat{\gamma} = \widehat{(\pi\tau)} = \hat{\lambda}_d / 4.$$

The period effect π is estimated using the contrast in the total response of both the periods and coincides with $\hat{\pi}$ in the parameterization numbers 1 and 2.

The estimation of $\hat{\tau}$ is the same as $\hat{\tau} = \dfrac{\overline{d}_{1o} - \overline{d}_{2o}}{4} = \dfrac{\hat{\tau}_d}{2}$ in parameterization No.$1(a)$ in the reduced model and in parameterization number 2. Furthermore, the estimates in $\hat{\beta}_3$ are independent, so that e.g., $H_0 : \tau = 0$ can be tested not depending on $\gamma = \lambda_d = 0$ (in contrast to parameterization number 1).

Parametrization number 4

Here, the main–effects treatment and sequence and their interaction are represented in a two-factorial model as

$$E(y_{ijk}) = \mu_{ij} = \mu + \gamma_i + \tau_t + (\gamma\tau)_{it},$$

i.e.,

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = X_4\beta_4 = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & -1 & -1 \\ 1 & -1 & -1 & 1 \\ 1 & -1 & -1 & 1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma \\ \pi \\ (\gamma\tau) \end{pmatrix}.$$

Since $X_4'X_4 = 4I_4$, the components of β_4 can be estimated independently as

$$\hat{\beta}_4 = \begin{pmatrix} \hat{\mu} \\ \hat{\gamma} \\ \hat{\tau} \\ \widehat{(\gamma\tau)} \end{pmatrix} = \begin{pmatrix} \overline{y}_{ooo} \\ (\overline{y}_{1oo} - \overline{y}_{2oo})/2 \\ \hat{\tau}_d/2 \\ (\overline{y}_{o1o} - \overline{y}_{o2o})/2 \end{pmatrix}.$$

Values of $\hat{\gamma}$ in the parameterization numbers 3 and 4 are the same. Analogously, the values of $\hat{\tau}$ coincide in parameterizations 2, 3 and 4 whereas the interaction effect *sequence* x *treatments* $(\widehat{\gamma\tau})$ refers to the period effect π in parameterizations 1, 2, and 3.

The resulting estimators from various parameterizations are compiled in the following table.

	Parameterizations					
	Classical	**Number 1**	**Number 1(a)**	**Number 2**	**Number 3**	**Number 4**
$\hat{\mu}$	$\overline{y}_{ooo}$	$\overline{y}_{ooo}$	$\overline{y}_{ooo}$	$\overline{y}_{ooo}$	$\overline{y}_{ooo}$	$\overline{y}_{ooo}$
$\hat{\gamma}$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\hat{\lambda}_d / 4$	$\hat{\lambda}_d / 4$
$\hat{\pi}$	$\hat{\pi}_d = (\overline{d}_{1o} + \overline{d}_{2o})/2$	$\hat{\pi}_d / 2$	$\hat{\pi}_d / 2$	$\hat{\pi}_d / 2$	$\hat{\pi}_d / 2$	$\cdot\ \cdot\ \cdot$
$\hat{\tau}$	$\hat{\tau}_d / \lambda_d = \overline{y}_{11o} - \overline{y}_{21o}$	$(\hat{\tau}_{d/\lambda_d})/2$	$\hat{\pi}_d / 2$	$\hat{\pi}_d / 2$	$\hat{\pi}_d / 2$	$\hat{\pi}_d / 2$
$\hat{\lambda}$	$\hat{\lambda}_d = 2(\overline{y}_{1oo} - \overline{y}_{2oo})$	$\lambda_d / 2$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$
$\widehat{(\tau\pi)}$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\hat{\lambda}_d / 4$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$
$\widehat{(\gamma\tau)}$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\cdot\ \cdot\ \cdot$	$\hat{\pi}_d / 2$

Remarks

From the various parameterizations we get the following remarks:

i. The estimators of τ and λ are correlated in the parameterization number1. $E(MS_{\text{Treat}})$ depends on $(\lambda_1 - \lambda_2) = 2\lambda$ so

that testing for $H_0 : \tau = 0$ may be done either using a central t - test if $\lambda = 0$ or using a non-central t - test if λ is

known. A difficulty in this case that τ and λ are correlated but it is not represented in the two-factorial hierarchy

"main effect A, main effect B, and the interaction $A \times B$".

ii. The carry-over effect is indirectly represented as the alias effect of the interaction $(\pi\tau)$ in parameterization no. 2. Since the design is orthogonal, so one can use the common hierarchical test procedure, as in a two-factorial model with interaction. If the interaction is not significant even then the estimators of the main effects remain the same. This does not hold in parameterization number 1.

iii. The analysis of data in a 2 x 2 cross-over design is conducted in two steps.

The first step is based on parameterization number 3 in which the carry over effect is tested in which the carry over

effect is separable from the main effect. This gives the same result as if the sequence effect is used.

Suppose we conduct the following experiment. Create two groups of subjects and apply the treatments to both the groups in same order, say *AB*. If interaction effect is present, then the two groups can be thought of having two different classes of subjects. Now there are two possibilities – either the subjects in the two groups are different or the treatment *A* has different effects in the two groups.

The possibility that the treatment *A* has different effects in the two groups is less, so it can be concluded that the subjects in both the groups react differently to the same treatment. So the sequence effect is present which is causing this difference but carry-over effect is absent.

Such confusion that is caused either by sequence effect or carry-over effect can be avoided by randomizing the subjects.

There are two ways to interpret a significant interaction effect in the classical designs.
  (a) If the randomization has not been done sufficiently, then it can be the true sequence effect.
  (b) If the randomization has been done properly, then this can be considered as the true carry-over effect.

In practice, it is very difficult to decide whether the randomization in a real data set has been done properly or not, so it is necessary to decide first that whether the effect is sequence effect or carry-over effect before starting the analysis of data.

The possibility of presence of sequence effect is more in case the randomization of subjects has not been done properly. Since there is no natural link between a sequence effect and a treatment or a period effect so the *F*-statistic in parameterization number 3 remains valid and this does not depend upon the presence or absence of the sequence effect.

If we are confident that the subjects have been properly randomized, then the interaction effect is regarded as a result of carry-over and there is no need to consider a sequence effect.

If the washout period between the two periods is not long enough, then the carry-over effect enters in the data and this can be considered as an additive term in the linear model. So if carry-over effect is significant, then the F-statistic in parameterization number 3 or classical approach does not remain valid.

We continue our analysis with the following possible options.

(a) Use the data of the first period only and test the significance of treatment effect. If the sample size is too small for a parallel group design then it is difficult to do so. In such case, we omit the sequence effect from the analysis (because we have only this first period).

(b) In case, the carry-over effect is significant, then it indicates that the two treatments have different effects. At least we can state that the two treatments have different effects and therefore these are not equal.

The expressions of *F*-statistic for carry-over effect, treatment effect and period effect in the analysis of variance remain valid only when the carry-over effect is not found to be significant. The expression for the treatment effect and period effect remain valid only when carry-over effect is not significant.

If the labels of "carry-over effect" is replaced by the label "sequence effect", then the importance of ordering is lost. Now nothing can be inferred to about the carry-over effect which is usually more important than the sequence effect. One needs to be careful in the interpretation of the results and the relabeling of the effect is to be accounted. The analysis of variance table obtained by the classical approach remains valid.

We have considered the 2 x 2 design. If a third period is to be added, there will be one baseline period and two washout periods. The set up of table will look like as follows:

Sequence	Period				
	1	2	3	4	5
1	Baseline	*A*	Washout	*B*	Washout
2	Baseline	*B*	Washout	*A*	Washout

The linear model then contains two additional period effects and carry-over effects of first and second order. The main advantages are that all parameters are estimable, there is no dependence between treatment and carry-over effects, and we get reduced variance