Analysis of Variance and Design of Experiments-II

MODULE VII

LECTURE - 31

CROSS-OVER DESIGNS

Dr. Shalabh
Department of Mathematics & Statistics
Indian Institute of Technology Kanpur

Analysis of variance

Now we develop the analysis of variance for higher order cross-over designs when $n_1 = n_2$. This is used to test the effects using F - test obtained from an analysis of variance table. The various sums of squares can be derived for the 2 x 2 cross-over design as a simple example of a split-plot design. The subject form the main plots and the periods are treated as the subplots at which repeated measurements are taken. Following this, the total sum of squares is given as

$$SS_{\text{Total}} = \sum_{i=1}^{2}\sum_{j=1}^{2}\sum_{k=1}^{n_i} y_{ijk}^2 - \frac{Y_{ooo}^2}{2(n_1+n_2)},$$

the sum of squares between subjects are given by:

$$SS_{\text{Carry-over}\,(c\text{-}o)} = \frac{2n_1 n_2}{(n_1+n_2)}(\bar{y}_{1oo} - \bar{y}_{2oo})^2 : \text{Sum of squares due to carry-over effect.}$$

$$SS_{\text{Residual}\,(b\text{-}s)} = \sum_{i=1}^{2}\sum_{k=1}^{n_i} \frac{Y_{iok}^2}{2} - \sum_{i=1}^{2} \frac{Y_{ioo}^2}{2n_i} : \text{Sum of squares due to between-subject residuals,}$$

the sum of squares within-subjects are given by

$$SS_{\text{Treat}} = \frac{n_1 n_2}{2(n_1+n_2)}(\bar{y}_{11o} - \bar{y}_{12o} - \bar{y}_{21o} + \bar{y}_{22o})^2 : \text{Sum of squares due to treatments effects.}$$

$$SS_{\text{Period}} = \frac{n_1 n_2}{2(n_1+n_2)}(\bar{y}_{11o} - \bar{y}_{12o} + \bar{y}_{21o} - \bar{y}_{22o})^2 : \text{Sum of squares due to period effects.}$$

$$SS_{\text{Residual}\,(w\text{-}s)} = \sum_{i=1}^{2}\sum_{j=1}^{2}\sum_{k=1}^{n_i} y_{ijk}^2 - \sum_{i=1}^{2}\sum_{j=1}^{2} \frac{Y_{ijo}^2}{n_i} - SS_{\text{Residual}\,(b\text{-}s)} : \text{Sum of squares due to within-subject residuals.}$$

Then the resulting analysis of variance and the construction of F statistics is given in the following Table:

Source	**Sum of squares**	**Degrees of freedom**	**Mean squares (*MS*)**	***F***	***E*(*MS*)**
Between–subjects					
Carry-out	$SS_{\text{carry-over}(c\text{-}o)}$	1	$MS_{\text{carry-over}(c\text{-}o)}$	F_{c-o}	$[(2n_1n_2)/(n_1+n_2)](\lambda_1-\lambda_2)^2+(2\sigma_s^2+\sigma^2)$
Residual (between subjects)	$SS_{\text{Residual}(b\text{-}s)}$	n_1+n_2-2	$MS_{\text{Residual}(b\text{-}s)}$		$(2\sigma_s^2+\sigma^2)$
Within–subjects					
Direct treatment effect	SS_{Treat}	1	MS_{Treat}	F_{Treat}	$(2n_1n_2)/(n_1+n_2)[(\tau_1-\tau_2)-(\lambda_1-\lambda_2)/2]^2+\sigma^2$
Period effect	SS_{Period}	1	MS_{Period}	F_{Period}	$[(2n_1n_2)/(n_1+n_2)](\pi_1-\pi_2)^2+\sigma^2$
Residual (within-subjects)	$SS_{\text{Residual}(w\text{-}s)}$	n_1+n_2-2	$MS_{\text{Residual}(w\text{-}s)}$		σ^2
Total	SS_{Total}	$2(n_1+n_2)-1$			

Under $H_0 : \lambda_1 = \lambda_2$ we have $E\left(MS_{\text{carry-over}(c-o)}\right) = E\left(MS_{\text{Residual}(b\text{-}s)}\right)$ and we use the statistic

$$F_{\text{c-o}} = \frac{MS_{\text{carry-over}(c-o)}}{MS_{\text{Residual(b-s)}}}.$$

Assuming $\lambda_1 = \lambda_2$ and $H_0 : \tau_1 = \tau_2$, we have $E(MS_{\text{Treat}}) = E(MS_{\text{Residual(w-s)}}) = \sigma^2$. Therefore, we get

$$F_{\text{Treat}} = \frac{MS_{\text{Treat}}}{MS_{\text{Residual}(w\text{-}s)}}$$

Testing for period effects does not depend upon the assumption that $\lambda_1 = \lambda_2$ holds. Since $E\left(MS_{\text{Period}}\right) = E\left(MS_{\text{Residual}}\right) = \sigma^2$

under $H_0 : \pi_1 = \pi_2$, so the statistic

$$F_{\text{Period}|\text{H}_0} = \frac{MS_{\text{Period}}}{MS_{\text{Residual}(w\text{-}s)}}$$

follows the central *F* - distribution with 1 and $(n_1 + n_2 - 2)$ degrees of freedom.

Comment on the procedure of testing

Usually, the carry-out effects are tested on a quite high level of significance $(\alpha = 0.1)$ first.

- If this leads to a significant result, then the test for treatment effects is to be based on the data of the first period only.
- If it is not significant, then the treatment effects are tested using the differences between the periods.

The hypothesis of no carry-over effect is very likely to be rejected even if there is a true carry-over effect. Hence, the biased test (biased, because the carry-over was not recognized) is used to test for treatment differences. This test is conservative in the case of a true positive carry-over effect and therefore this is insensitive to potential differences in treatments.

On the other hand, this test will exceed the level of significance if there is a true negative carry-over effect (not very likely in practice, since this refers to a withdrawal effect).

If there is no true carry-over effect, the null hypothesis is very likely to be rejected erroneously $(\alpha = 0.1)$ and the less efficient test using first-period data only is performed.

This method is not very useful in testing treatment effects as it depends upon the outcome of the pretest.

Alternative parameterization in 2 x 2 Cross-Over

The model

$$y_{ijk} = \mu + s_{ik} + \pi_j + \tau_{[i,j]} + \lambda_{[i,j-1]} + \varepsilon_{ijk}$$

is used in the classical approach and is labeled as parameterization number 1. A more general parameterization of the 2 x 2 cross-over design, includes a sequence effect γ_i and is given by

$$y_{ijk} = \mu + \gamma_i + s_{ik} + \pi_j + \tau_t + \lambda_r + \varepsilon_{ijk},$$

with *i, j, t, r* = 1, 2 and $k = 1,\dots,n_{i\cdot}$. The data are summarized in a table containing the cell means $\overline{y}_{ijo}$, i.e.,

		Period	
		1	**2**
Sequence	**1**	$\overline{y}_{11o}$	$\overline{y}_{12o}$
	2	$\overline{y}_{21o}$	$\overline{y}_{22o}$

Here Sequence 1 indicates that the treatments are given in the order (*AB*) and Sequence 2 has the (*BA*) order. Using the common restrictions

$$\gamma_2 = -\gamma_1,\ \pi_2 = -\pi_1,\quad \tau_2 = -\tau_1,\ \lambda_2 = -\lambda_1$$

and writing $\gamma_1 = \gamma,\ \pi_1 = \pi,\ \tau_1 = \tau,\ \lambda_1 = \lambda$ for brevity, we get the following equations representing the four expectations:

$$\begin{aligned}
\mu_{11} &= \mu + \gamma + \pi + \tau \\
\mu_{12} &= \mu + \gamma - \pi - \tau + \lambda, \\
\mu_{21} &= \mu - \gamma + \pi - \tau, \\
\mu_{22} &= \mu - \gamma - \pi + \tau - \lambda.
\end{aligned}$$

In matrix notation, we can express it as

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = X\beta = \begin{pmatrix} 1 & 1 & 1 & 1 & 0 \\ 1 & 1 & -1 & -1 & 1 \\ 1 & -1 & 1 & -1 & 0 \\ 1 & -1 & -1 & 1 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma \\ \pi \\ \tau \\ \lambda \end{pmatrix}.$$

The *X* matrix is of order (4 x 5) and has rank 4, so that β is only estimable if one of the parameters is removed. Various parameterizations are possible depending on which of the five parameters is to be removed and then to be confounded with the remaining ones.

Parametrization Number 1

The classical approach ignores the sequence parameter. Its expectations may therefore be represented as a submodel of

$$\begin{pmatrix} \mu_{11} \\ \mu_{12} \\ \mu_{21} \\ \mu_{22} \end{pmatrix} = X\beta = \begin{pmatrix} 1 & 1 & 1 & 1 & 0 \\ 1 & 1 & -1 & -1 & 1 \\ 1 & -1 & 1 & -1 & 0 \\ 1 & -1 & -1 & 1 & -1 \end{pmatrix} \begin{pmatrix} \mu \\ \gamma \\ \pi \\ \tau \\ \lambda \end{pmatrix}$$

by dropping the second column of X as

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

We obtain from this

$$X_1^{'}X_1 = \begin{pmatrix} E & 0 \\ 0 & H \end{pmatrix},$$

where

$$E = 4I_2,$$

$$H = \begin{pmatrix} 4 & -2 \\ -2 & 2 \end{pmatrix},$$

$$\left| X_1^{'}X_1 \right| = 64,$$

$$(X_1^{'}X_1)^{-1} = \begin{pmatrix} E^{-1} & 0 \\ 0 & H^{-1} \end{pmatrix}$$

with $E^{-1} = \frac{1}{4} I_2$, $H^{-1} = \begin{pmatrix} 1/2 & 1/2 \\ 1/2 & 1 \end{pmatrix}$. The least squares estimate of β_1 is obtained as

$$\hat{\beta}_1 = \begin{pmatrix} \hat{\mu} \\ \hat{\pi} \\ \hat{\tau} \\ \hat{\lambda} \end{pmatrix} = (X_1^{'} X_1)^{-1} X_1^{'} \begin{pmatrix} \bar{y}_{11o} \\ \bar{y}_{12o} \\ \bar{y}_{21o} \\ \bar{y}_{22o} \end{pmatrix}.$$

Observe that

$$X_1^{'} \begin{pmatrix} \bar{y}_{11o} \\ \bar{y}_{12o} \\ \bar{y}_{21o} \\ \bar{y}_{22o} \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & -1 & 1 & -1 \\ 1 & -1 & -1 & 1 \\ 0 & 1 & 0 & -1 \end{pmatrix} \begin{pmatrix} \bar{y}_{11o} \\ \bar{y}_{12o} \\ \bar{y}_{21o} \\ \bar{y}_{22o} \end{pmatrix}$$

$$= \begin{pmatrix} \bar{y}_{11o} & + & \bar{y}_{12o} & + & \bar{y}_{21o} & + & \bar{y}_{22o} \\ \bar{y}_{11o} & - & \bar{y}_{12o} & + & \bar{y}_{21o} & - & \bar{y}_{22o} \\ \bar{y}_{11o} & - & \bar{y}_{12o} & - & \bar{y}_{21o} & + & \bar{y}_{22o} \\ & & \bar{y}_{12o} & - & \bar{y}_{22o} & & \end{pmatrix}.$$

Therefore, the least squares estimates are given as

$$\hat{\beta}_1 = \begin{pmatrix} \hat{\mu} \\ \hat{\pi} \\ \hat{\tau} \\ \hat{\lambda} \end{pmatrix} = (X_1^{'} X_1)^{-1} X_1^{'} \begin{pmatrix} \bar{y}_{11o} \\ \bar{y}_{12o} \\ \bar{y}_{21o} \\ \bar{y}_{22o} \end{pmatrix}$$

$$= \begin{pmatrix} (\bar{y}_{11o} & + & \bar{y}_{12o} & + & \bar{y}_{21o} & + & \bar{y}_{22o})/4 \\ (\bar{y}_{11o} & - & \bar{y}_{12o} & + & \bar{y}_{21o} & - & \bar{y}_{22o})/4 \\ & & (\bar{y}_{12o} & - & \bar{y}_{21o})/2 & & \\ (\bar{y}_{11o} & + & \bar{y}_{12o} & - & \bar{y}_{21o} & - & \bar{y}_{22o})/2 \end{pmatrix}$$

from which we get the following estimators:

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

$$\hat{\pi} = \frac{(\bar{y}_{o1o} - \bar{y}_{o2o})}{2} = \frac{(\bar{c}_{1o} - \bar{c}_{2o})}{4} = \frac{\hat{\pi}_d}{2}$$

$$\hat{\tau} = \frac{(\bar{y}_{11o} - \bar{y}_{21o})}{2} = \frac{\hat{\tau}_{d/\lambda_d}}{2}$$

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

The covariance between $\hat{\tau}$ and $\hat{\lambda}$ is

$$Cov(\hat{\tau},\hat{\lambda}) = \sigma^2 H^{-1} = \sigma^2 \begin{pmatrix} 1/2 & 1/2 \\ 1/2 & 1 \end{pmatrix}.$$

Hence $\hat{\tau}$ and $\hat{\lambda}$ are correlated. The correlation coefficient

$$\rho(\hat{\tau},\hat{\lambda}) = \frac{1}{2} \Big/ \left(\frac{1}{2}.1\right)^{1/2} = 0.707.$$

The estimation of $\hat{\tau}$ is always twice as accurate as the estimation of $\hat{\lambda}$. Note that $\hat{\tau}$ uses the data of the first period only and is confounded with the difference between the two groups (sequences).

Remark

In fact, parameterization number 1 is a three-factorial design with the main effects π, τ and λ and with τ and being λ correlated. On the other hand, the classical approach uses the split-plot model in addition to the classical parameterization. So it is obvious that we will get different results depending on which of the parameterization is used.