ST4241: Design and Analysis of Clinical Trials

2009/2010: Semester I

Tutorial 10

1. The following data is from the two-period crossover study considered in Lecture notes 8. In each square, the treatments in the first row are (A, B) and in the second row are (B, A).

		Period	
Square	Patient	1	2
1	1	5.1	3.8
	2	2.9	3.9
2	1	0.6	1.0
	2	2.9	3.9
3	1	4.8	3.1
	2	4.0	5.8
4	1	4.4	4.9
	2	1.6	0.8
5	1	2.3	1.3
	2	4.1	4.7
6	1	4.9	2.3
	2	3.2	0.9
7	1	6.8	4.5
	2	2.3	4.0
8	1	6.1	2.2
	2	3.4	3.6

(i) Using the linear model approach, derive the following ANOVA table:

Source	df	SS	MS	F ratio
Patients				
Periods				
Treatments				
Residuals				

(ii) Confirm that the F ratios for Periods and Treatments are the squares of the corresponding t statistics given in the lecture notes.

(iii) Confirm that the residual mean sum of squares is half the value of s_D^2 given in the lecture notes. Argue why?

2. For the crossover study with g period and q Latin squares, assume that the observation of Patient l in Period i on Treatment j when Treatment k was given in the preceding period, X_{ijkl}, has expectation:

$$E(X_{ijkl}) = \mu + \pi_i + \tau_j + \rho_k + \nu_l,$$

where the parameters satisfy $\sum \pi_i = \sum \tau_j = \sum \rho_k = 0$. Let $d_{ijkl} = X_{ijkl} - \bar{X}_{\cdots l}$, where $\bar{X}_{\cdots l}$ is the mean response of Patient l.

(i) Let $\bar{t}_i$ denote the mean of all qg d's for Treatment i. Show that

$$\bar{t}_i = \frac{1}{qg^2}(gT_i - G),$$

and that

$$E(\bar{t}_i) = \tau_i - \rho_i/g.$$

(ii) Let $\bar{r}_i$ denote the mean of all $q(g-1)$ d's in the periods immediately after the administration of Treatment i. Show that

$$\bar{r}_i = \frac{1}{qg(g-1)}(gR_i - G + F_i),$$

and that

$$E(\bar{r}_i) = \frac{g^2 - g - 1}{g(g-1)}\rho_i - \frac{\tau_i}{g-1} - \frac{\pi_i}{g-1}.$$

(iii) Let $\bar{p}_1$ denote the mean of all qg d's in Period 1. Show that

$$\bar{p}_1 = \frac{1}{qg^2}(gP_1 - G),$$

and that $E(\bar{p}_1) = \pi_1$. Thus show that

$$E(\bar{r}_i + \frac{\bar{p}_1}{g-1}) = \frac{g^2 - g - 1}{g(g-1)}\rho_i - \frac{\tau_i}{g-1}.$$

(iv) Let $\hat{\tau}_i$ and $\hat{\rho}_i$ be defined through the following equations:

$$\begin{aligned} \hat{\tau}_i - \frac{1}{g}\hat{\rho}_i &= \bar{t}_i \\ \frac{g^2 - g - 1}{g(g-1)}\hat{\rho}_i - \frac{1}{g-1}\hat{\tau}_i &= \bar{r}_i + \frac{\bar{p}_1}{g-1}. \end{aligned}$$

Show that $\hat{\tau}_i$ and $\hat{\rho}_i$ are unbiased estimators of τ_i and ρ_i respectively, and that they are equal to the unbiased estimators given in the lecture notes.

3. For the example of crossover study with four periods discussed in Lecture notes 8, using the R code given in the lecture notes, find the differences between the estimated direct effects of Treatments 1, 2, and 3 and the estimated direct effect of Treatment 4. Find the estimated standard deviations of the differences. Confirm that none of the differences are significant compared with the Dunnett criterion for two-tailed tests with an overall significance level 0.05.