ST4241: Design and Analysis of Clinical Trials

2009/2010: Semester I

Tutorial 3

1. The following table gives the summary data from a drug trial, with higher values being associated with better responses.

Drug A	Drug B	n_i	$\bar{X}_i$	s_i
no	no	15	12.2	6.66
yes	n0	14	19.3	8.45
no	yes	13	20.6	11.39
yes	yes	15	38.5	9.72

It is required to test the effect of each drug (in the absence of the other) and the interaction effect.

(i) Give the test statistics for the three tests (two for the effects of Drug A and B, one for the interaction).

The pooled estimate of the error variance is

$$\begin{aligned} s^2 &= \frac{14 \times 6.66^2 + 13 \times 8.45^2 + 12 \times 11.39^2 + 14 \times 9.72^2}{14 + 13 + 12 + 14} = 83.5603. \\ s &= 9.1411. \end{aligned}$$

The test statistic for the effect of Drug A is

$$\begin{aligned} L_{A|\bar{B}} &= \frac{\hat{E}_{A|\bar{B}}}{\sqrt{\widehat{Var}(\hat{E}_{A|\bar{B}})}} = \frac{\bar{X}_2 - \bar{X}_1}{s}\sqrt{\frac{n_1 n_2}{n_1 + n_2}} \\ &= \frac{19.3 - 12.2}{9.1411} \times \sqrt{15 \times 14/(15 + 14)} = 2.09. \end{aligned}$$

The test statistic for the effect of Drug B is

$$\begin{aligned} L_{B|\bar{A}} &= \frac{\hat{E}_{B|\bar{A}}}{\sqrt{\widehat{Var}(\hat{E}_{B|\bar{A}})}} = \frac{\bar{X}_3 - \bar{X}_1}{s}\sqrt{\frac{n_1 n_3}{n_1 + n_3}} \\ &= \frac{20.6.3 - 12.2}{9.1411} \times \sqrt{15 \times 13/(15 + 13)} = 2.43. \end{aligned}$$

The test statistic for the interaction effect is

$$L_{AB} = \frac{\hat{E}_{AB}}{\sqrt{\widehat{Var}(\hat{E}_{AB})}} = \frac{\bar{X}_4 - \bar{X}_3 - \bar{X}_2 + \bar{X}_1}{s} / \sqrt{1/n_1 + 1/n_2 + 1/n_3 + 1/n_4}$$

$$= \frac{38.5 - 20.6 - 19.3 + 12.2}{9.1411} / \sqrt{1/15 + 1/14 + 1/13 + 1/15} = 2.23.$$

(ii) Conduct the three tests controlling the overall error rate at $\alpha = 0.05$ by using an appropriate procedure. Give your conclusion of the tests.

The Bonferroni criterion is appropriate in this case. The critical value of the Bonferroni criterion is $t_{53,0.05/6} = 2.4723$*. By comparing the values of the statistics in part (i) with this critical value, none of the tests are significant.*

2. Let $Y_1, \ldots, Y_m$ denote m independent estimators of the same underlying parameter, and suppose that $\text{Var}(Y_j) = \sigma^2/w_j, j = 1, \ldots, m$, where w_j's are known constants. Let $\nu_1, \ldots, \nu_m$ be any nonnegative weights satisfying $\sum_{j=1}^m \nu_j = 1$.

(i) Prove that the weighted average $\bar{Y}_{opt} = (\sum_{j=1}^m w_j Y_j)/\sum_{j=1}^m w_j$ has the smallest variance among all weighted averages of the form $\bar{Y} = \sum_{j=1}^m \nu_j Y_j$.

The variance of $\bar{Y} = \sum_{j=1}^m \nu_j Y_j$ *is given by*

$$V(\boldsymbol{\nu}) = \sigma^2 \sum_{j=1}^m \nu_j^2 / w_j.$$

Note that $\nu_m = 1 - \sum_{j=1}^{m-1} \nu_j$*. Differentiating* $V(\boldsymbol{\nu})$ *with respect to* $\nu_j, j = 1, \ldots, m-1$*, and setting the derivatives to zero, we have*

$$\frac{\nu_j}{w_j} = \frac{\nu_m}{w_m}, \quad j = 1, \ldots, m-1.$$

Summing up both sides of the above equation yields

$$1 - \nu_m = \nu_m \frac{\sum_{j=1}^{m-1} w_j}{w_m}.$$

It solves for

$$\nu_m = \frac{w_m}{\sum_{j=1}^m w_j},$$

Hence

$$\nu_j = \frac{w_j}{w_m}\nu_m = \frac{w_j}{\sum_{j=1}^m w_j}.$$

(ii) Show that $\text{Var}(\bar{Y}_{opt}) = \sigma^2 / \sum_{j=1}^m w_j$.

Substituting $\nu_j = \frac{w_j}{\sum_{j=1}^m w_j}$ *into the* $V(\boldsymbol{\nu})$*, the result follows.*

3. In a 2×2 factorial design, the test for interaction when σ^2 is known and all four sample sizes are equal to n declares the interaction to be statistically significant if $|\hat{E}_{AC}|/\sqrt{4\sigma^2/n} > z_{\alpha/2}$, where $\hat{E}_{AC}$ is the estimated interaction effect.

(i) Suppose the true interaction effect $E_{AC} = \Delta > 0$. Show that the power of the above test is

$$Pr(Z > z_{\alpha/2} - \Delta/\sqrt{4\sigma^2/n}),$$

where Z is a standard normal random variable.

When $\Delta > 0$,

$$\begin{aligned} Pr(\hat{E}_{AC}/\sqrt{4\sigma^2/n} > z_{\alpha/2}) &= Pr((\hat{E}_{AC} - \Delta)/\sqrt{4\sigma^2/n} > z_{\alpha/2} - \Delta/\sqrt{4\sigma^2/n}) \\ &= Pr(Z > z_{\alpha/2} - \Delta/\sqrt{4\sigma^2/n}). \end{aligned}$$

Similarly,

$$\begin{aligned} Pr(\hat{E}_{AC}/\sqrt{4\sigma^2/n} < -z_{\alpha/2}) &= Pr((\hat{E}_{AC} - \Delta)/\sqrt{4\sigma^2/n} < -z_{\alpha/2} - \Delta/\sqrt{4\sigma^2/n}) \\ &= Pr(Z < -z_{\alpha/2} - \Delta/\sqrt{4\sigma^2/n}). \end{aligned}$$

The second probability is approximately zero, hence the result follows.

(ii) Show that if the power of the above test is required to be $1-\beta$ then the required sample size is

$$n = \frac{4\sigma^2(z_{\alpha/2}+z_\beta)^2}{\Delta^2}.$$

For the power to be $1-\beta$*, it must be hold that*

$$z_{\alpha/2} - \Delta/\sqrt{4\sigma^2/n} = z_\beta,$$

which yields the required sample size.

4. The following table gives the results of a reliability study comparing DMFS scores (number of decayed, missing, and filled surfaces of a patient's permanent teeth) by four examiners on ten patients.

	Examiner			
Patient	1	2	3	4
1	8	7	11	7
2	13	11	15	13
3	0	0	2	1
4	3	6	9	6
5	13	13	17	10
6	19	23	27	18
7	0	0	1	0
8	2	0	4	5
9	18	20	22	16
10	5	3	8	3

(i) It is of concern whether or not each examiner's score is consistent with the other's. State the contrasts which are appropriate for testing the consistency of scores among examiners.

The appropriate contrasts are the difference of each examiner's mean score and the average score of the other three examiners, i.e,

$$C_j = \bar{X}_j - \frac{1}{3}[\sum_{i=1}^{4} \bar{X}_i - \bar{X}_j], j = 1, \ldots, 4.$$

(ii) Using Bonferroni's criterion to control overall error rate at level $\alpha = 0.05$, conduct the hypothesis testing of the contrasts you stated in part (i). Give your conclusion.

The residual sum of squares is computed as:

$$RSS = \sum (X_{ij} - \bar{X}_{i\cdot} - \bar{X}_{\cdot j} + \bar{X}_{\cdot\cdot})^2 = 74.575.$$

The mean residual sum of squares is then $RMS = 74.575/27 = 2.7620.$

The test statistics are given by

$$L_j = \frac{C_j}{\sqrt{RMS(\frac{1}{n_j} + \frac{1}{9}[\sum_{i=1}^{4} \frac{1}{n_i} - \frac{1}{n_j}])}}, \; j = 1, \ldots, 4.$$

They are computed as

$$L_1 = -1.9225, L_2 = -1.4831, L_3 = 5.7675, L_4 = -2.3619.$$

The critical value of the Bonferroni criterion is $t_{27,0.05/8} = 2.676258$*. By Bonferroni's criterion, only* L_3 *is significant, meaning that examiner 3 does not have consistent scores with the others.*

(iii) If, instead of Bonferroni's criterion, you use other criterion such as Scheffe's, Tukey's and Dunnett's criterion to control the overall error rate at the same level, what will be your conclusion on the tests?

The Scheffe's critical value is $\sqrt{3F_{3,27,0.05}} = 2.9801$.

The Tukey's critical value is $q_{3,27,0.05}$ *which is in between 3.486 and 3.532.*

Dunnett's critical value is $d_{3,27,0.05}$ *which is in between 2.47 and 2.51.*

By using any of these criteria, only L_3 *can be claimed significant. But except Scheffe's criterion, the other two are not designed for the type of contrasts considered in this problem. Bonferroni's criterion, compared with Scheffe's, have higher power for the tests.*