

# ST4241: Design and Analysis of Clinical Trials

2009/2010: Semester I

## Tutorial 1

1. The following three questions pertain to different aspects of the multiple comparison artifact.
- (a) If each of  $K$  contrasts was tested for significance at the  $\alpha$  significance level, how many contrasts would you expect, just by chance, to find significant? What is this expected number when  $K = 100$  and  $\alpha = 0.05$ ?

*About  $K\alpha$  contrasts would be expected to be found significant. For  $K = 100$ , about 5 will be bound significant.*

- (b) Suppose that the ratios  $\hat{C}/\text{se}(\hat{C})$  for each of  $K$  contrasts are mutually independent and that each is tested for significance at the  $\alpha$  significance level. Show that the probability that at least one is erroneously found to be significant is equal to  $1 - (1 - \alpha)^K$ . What is this probability if  $K = 14$  and  $\alpha = 0.05$ ?

*Let  $A_k$  denote the event that the  $k$ th contrast is erroneously found to be significant. The probability that at least one is erroneously found to be significant is given by*

$$P(\cup_{k=1}^K A_k) = 1 - P(\cap_{k=1}^K A_k^C) = 1 - \prod_k P(A_k^C) = 1 - (1 - \alpha)^K.$$

*For  $K = 14$  and  $\alpha = 0.05$ , this probability is given by*

$$1 - 0.95^{14} = 0.512325.$$

- (c) Investigators will occasionally single out the smallest and the largest of  $g$  means for a  $t$  test at the  $\alpha$  significance level. That is, when the sample sizes are all equal to a common  $n$ , the largest and smallest means are declared to differ significantly if

$$L = \frac{\max \bar{X}_i - \min \bar{X}_i}{\sqrt{\text{WMS}}} \sqrt{\frac{n}{2}}$$

exceeds  $t_{n-g, \alpha/2}$ . The correct critical values of  $L$  are given by the entries in Table A.5 of Fleiss divided by  $\sqrt{2}$ . Suppose that  $g = 4$ ,  $n = 7$  and  $L = 2.1$ . What would the verdict

be, significant or not, if  $L$  was compared to  $t_{24,0.025}$ ? Check that  $L$  would have to exceed 2.76 in order for significance to be declared using the correct test criterion.

$t_{24,0.025} = 2.063899$ . Since  $L = 2.1 > 2.063899$ , the contrast will be declared significant. Since the  $L$  above is the studentized range divided by  $\sqrt{2}$  and the critical value of the studentized range is  $q_{4,24} = 3.901$ , for  $L$  to be declared significant according to correct critical values,  $L$  must be larger than  $q_{4,24}/\sqrt{2} = 2.7584$ .

2. Prove that when  $g = 2$  the ratio  $F = \text{BMS}/\text{WMS}$  of mean squares from the analysis of variance table is identical to the square of the  $t$  ratio given by

$$t = \frac{\bar{X}_1 - \bar{X}_2}{s} \sqrt{\frac{n_1 n_2}{n_1 + n_2}},$$

where

$$s^2 = \frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}.$$

Note that  $s^2$  is in fact WMS. When  $g = 2$ , we have

$$\bar{X} = \frac{n_1 \bar{X}_1 + n_2 \bar{X}_2}{n_1 + n_2}.$$

Therefore,

$$\begin{aligned} n_1(\bar{X}_1 - \bar{X})^2 &= n_1 \left[ \frac{n_2(\bar{X}_1 - \bar{X}_2)}{n_1 + n_2} \right]^2, \\ n_2(\bar{X}_2 - \bar{X})^2 &= n_2 \left[ \frac{n_1(\bar{X}_1 - \bar{X}_2)}{n_1 + n_2} \right]^2. \end{aligned}$$

Hence,

$$\text{BMS} = n_1 \left[ \frac{n_2(\bar{X}_1 - \bar{X}_2)}{n_1 + n_2} \right]^2 + n_2 \left[ \frac{n_1(\bar{X}_1 - \bar{X}_2)}{n_1 + n_2} \right]^2 = \frac{n_1 n_2}{n_1 + n_2} (\bar{X}_1 - \bar{X}_2)^2.$$

It is then clear that  $t^2 = \frac{\text{BMS}}{\text{WMS}}$ .

3. The following table gives the 12 means and standard deviations of the survival times of 12 groups of animals, each receiving a combination of poisons and treatment.

Group	$X_i$	$s_i$
1	4.125	0.695
2	8.800	1.608
3	5.675	1.567
4	6.100	1.128
5	3.200	0.753
6	8.150	3.363
7	3.750	0.569
8	6.675	2.710
9	2.100	0.216
10	3.350	0.465
11	2.350	0.129
12	3.250	0.265

(i) Confirm that, of the values  $k = 1/2, 1, 2$  and  $3$ , the smallest ratio

$$R_k = \frac{\max(\frac{s_i}{\bar{X}_i^k})}{\min(\frac{s_i}{\bar{X}_i^k})}$$

is achieved when  $k = 2$ , thus indicating that  $s$  is more nearly proportional to  $\bar{X}^2$  than to the other powers of  $\bar{X}$ .

*The ratio  $R_k$  for  $k = 1/2, 1, 2$  and  $3$  are computed as follows:*

13.998848   7.517050   3.541395   9.884571

*$k = 2$  corresponds to the smallest  $R_k$ .*

(ii) Can you suggest any other way to determine an appropriate transformation of the original data (which is not given above)?

*We may transform the original data to any their powers to see which transformation produces the smallest variation of the standard deviations.*

4. Lysozyme levels in the gastric juice of 29 patients with peptic ulcer and of 30 normal controls are given below.

Patient group:

0.2   0.3   0.4   1.1   2.0   2.1   3.3   3.8   4.5   4.8   4.9   5.0   5.3   7.5   9.8   10.4  
 10.9   11.3   12.4   16.2   17.6   18.9   20.7   24.0   25.4   40.0   42.2   50.0   60.0

Control group:

0.2 0.3 0.4 0.7 1.2 1.5 1.5 1.9 2.0 2.4 2.5 2.8 3.6 4.8 4.8 5.4 5.7  
5.8 7.5 8.7 8.8 9.1 10.3 15.6 16.1 16.5 16.7 20.0 20.7 33.0

- (i) Apply  $t$  test to the transformed values of  $Y = \ln(X)$  to compare the two groups above. Compare the result with that of the  $t$  test applied to the original data. Make comments on the comparison.

*For the original data:*

$t = 2.0569$ ,  $df = 57$ ,  $p\text{-value} = 0.04428$

*For the log-transformed data:*

$t = 1.4088$ ,  $df = 57$ ,  $p\text{-value} = 0.1643$

*For the original data, the standard deviations of the two groups are from equal. The ratio of the two standard deviations is 2.005. The result of the  $t$  test is doubtful.*

*For the transformed data, the standard deviations of the two groups are almost equal. The ratio of the two standard deviations is 1.126. The result is more trustful.*

- (ii) Apply Mann-Whitney-Wilcoxon test to the above data. Are the two groups significantly different at level  $\alpha = 0.05$  according to this test?

*The following code in R*

```
wilcox.test(x1, x2, alternative = "two.sided", conf.level = 0.95)
```

*yields:*

$W = 541$ ,  $p\text{-value} = 0.1080$

*The test is not significant at  $\alpha = 0.05$*