

ST4241: Design and Analysis of Clinical Trials

2009/2010: Semester I

Tutorial 8

1. Consider the study comparing two groups of subjects with respect to the temperature of the forehead (in degrees Celsius) measured at 30-minute intervals. The summary data of the two groups are given below:

Group 1				
Subject	Time			
	1	2	3	4
1	30.9	30.7	30.9	30.9
2	31.9	31.6	31.6	31.7
3	31.3	31.1	31.0	31.3
4	32.1	31.0	31.7	31.3
5	30.9	31.2	30.5	30.8
6	31.3	31.7	31.4	31.2
7	31.3	31.8	31.8	31.7
8	32.1	33.0	31.7	31.5
9	30.3	30.9	30.8	30.6
10	32.2	32.1	32.2	32.4

Group 2				
Subject	Time			
	1	2	3	4
1	31.5	30.6	30.8	31.0
2	31.2	31.2	31.1	31.3
3	31.3	31.3	31.5	31.4
4	30.4	30.8	30.4	30.2
5	30.7	30.9	30.9	30.9
6	29.8	30.8	30.9	30.8
7	31.4	32.0	31.7	31.6
8	30.9	32.4	31.8	31.9
9	31.1	31.3	31.2	31.2
10	31.5	31.5	31.6	31.7

- (i) Compute the estimates of the variance-covariance matrix of the repeated measurements over time: (a) separately for each group and (b) a pooled estimate assuming the variance-covariance matrices of the two groups are the same.

The matrices are computed using the following R code:

```
x11 = c(30.9,31.9,31.3,32.1,30.9,31.3,31.3,32.1,30.3,32.2)
x12 = c(30.7,31.6,31.1,31.0,31.2,31.7,31.8,33.0,30.9,32.1)
x13 = c(30.9,31.6,31.0,31.7,30.5,31.4,31.8,31.7,30.8,32.2)
x14 = c(30.9,31.7,31.3,31.3,30.8,31.2,31.7,31.5,30.6,32.4)
x21 = c(31.5,31.2,31.3,30.4,30.7,29.8,31.4,30.9,31.1,31.3)
x22 = c(30.6,31.2,31.3,30.8,30.9,30.8,32.0,32.4,31.3,31.5)
x23 = c(30.8,31.1,31.5,30.4,30.9,30.9,31.7,31.8,31.2,31.6)
x24 = c(31.0,31.3,31.4,30.2,30.9,30.8,31.6,31.9,31.2,31.7)
X1=cbind(x11,x12,x13,x14)
X2=cbind(x21,x22,x23,x24)
S1 = var(X1)
S2= var(X2)
S = (S1+S2)/2
```

The computed matrices are as follows:

S1:

```
0.4001 0.2697 0.2813 0.2664
0.2697 0.4721 0.2349 0.2207
0.2813 0.2349 0.2871 0.2518
0.2664 0.2207 0.2518 0.2738
```

S2:

```
0.2804 0.0969 0.1173 0.1544
0.0969 0.3218 0.2276 0.2333
0.1173 0.2276 0.2054 0.2178
0.1544 0.2333 0.2178 0.2489
```

S:

```
0.3403 0.1833 0.1993 0.2104
0.1833 0.3969 0.2312 0.2270
0.1993 0.2312 0.2463 0.2348
0.2104 0.2270 0.2348 0.2613
```

- (ii) Compute the estimated correlation matrix based on the pooled estimate of the common variance-covariance matrix.

The correlation matrix is obtained by dividing the pooled variance matrix with the standard deviations. It is computed by

```
sd.inv = diag( sqrt(diag(S))^{-1} )
R = sd.inv%*%S%*%sd.inv
```

The correlation matrix is:

```
1.00 0.50 0.69 0.71
0.50 1.00 0.74 0.70
0.69 0.74 1.00 0.93
0.71 0.70 0.93 1.00
```

(iii) Compute the value of ϵ as expressed below:

$$\epsilon = \frac{(t-1)(1-\bar{\rho}_{..})^2}{(t-1)[(1-\bar{\rho}_{..})^2 - \frac{2(t-1)}{t} \sum (\bar{\rho}_{j.} - \bar{\rho}_{..})^2] + \sum \sum_{j \neq j'} (\rho_{jj'} - \bar{\rho}_{..})^2}$$

To compute ϵ , the quantities $\rho_{j.}$ and $\rho_{..}$ are first computed. The computation is done by

```
rho.j = apply(R,1,sum)
for (j in 1:4) {
  rho.j[j] = rho.j[j]-R[j,j]
}
rho.j = rho.j/3
rho = mean(rho.j)
a1 = (4-1)*(1-rho)^2
a2 = 2*(4-1)^2/4*sum((rho.j-rho)^2)
R.tmp = R
for (j in 1:4) {
  R.tmp[j,j] = rho
}
R.tmp = (R.tmp - rho)^2
a3 = apply(R.tmp, 1, sum)
a3 = sum(a3)
ep = a1/(a1-a2+a3)
```

The computed value is $\epsilon = 0.7298$.

(iv) Give the adjusted degrees of freedom for the F-ratios F_2 and F_3 for testing the significance of time effect and time by group interaction effect respectively.

The adjusted degrees of freedom of F_2 are:

$$(t-1)\epsilon = 3 \times 0.7298 = 2.1894, \quad (n-g)(t-1)\epsilon = 18.1894 = 39.4092.$$

The adjusted degrees of freedom of F_3 are:

$$(g-1)(t-1)\epsilon = 1 \times 3 \times 0.7298 = 2.1894, \quad (n-g)(t-1)\epsilon = 18.1894 = 39.4092.$$

2. Calculate the value of $C_i^{(k)} = -3X_{i1}^{(k)} - X_{i2}^{(k)} + X_{i3}^{(k)} + 3X_{i4}^{(k)}$ for each subject in the tables given in Problem 1 and confirm the values in the following table:

	n	Mean	sd
Group 1	10	-0.42	1.2943
Group 2	10	0.63	1.3565

Compute the weighted average of the two means and the pooled standard deviation.

The computation is done by

```

l = c(-3, -1, 1, 3)
C1 = X1%*%l
C2 = X2%*%l
c1.m= mean(C1)
c1.sd = sqrt(var(C1))
c2.m= mean(C2)
c2.sd = sqrt(var(C2))

```

Since the two groups have the same sample size, the weighted average of the two means and the pooled standard deviation are computed by

```

c.m = (c1.m+c2.m)/2
c.sd = sqrt((c1.sd^2+c2.sd^2)/2 )

```

The computed values:

0.105000, 1.325384

3. Apply the following two methods to the data in Problem 1 for testing whether the linear variation with time of the means in Group 1 is the same as in Group 2 (the vector of constants defining the contrast is $\mathbf{c} = (-3, -1, 1, 3)'$).

- (i) Method 1: With $\bar{\mathbf{X}}^{(1)}$ and $\bar{\mathbf{X}}^{(2)}$ denoting the two vectors of mean responses and with $\bar{\mathbf{S}}$ denoting the pooled covariance matrix, calculate $C = \mathbf{c}'(\bar{\mathbf{X}}^{(1)} - \bar{\mathbf{X}}^{(2)})$ and $\text{se}(C) = \sqrt{n \cdot \mathbf{c}' \bar{\mathbf{S}} \mathbf{c} / n_1 n_2}$, and find the value of $L = C / \text{se}(C)$.

The computation is done by

```
X1.m = apply(X1,2,mean)
X2.m = apply(X2,2,mean)
C = t(1)%*%(X1.m-X2.m)
C.se = sqrt( 20/10/10 * t(1)%*%S%*% 1 )
L1 = C/C.se
```

It yields $L1 = -1.770977$.

- (ii) Method 2: With $\mathbf{X}_i^{(k)}$ denoting the vector of t responses for Subject i in Group k , calculate the value of $C_i^{(k)} = \mathbf{c}' \mathbf{X}_i^{(k)}$ separately for each subject and compare the resulting means in the straightforward way of two-sample t test.

The computation is done by

```
L2 = (c1.m-c2.m)/c.sd /sqrt(20/10/10)
```

It yields the same value as $L1$.

Confirm that, no matter which method is employed, the same t -statistic value is found.