4. Blocking to control prognostic variables

§4.1. Complete randomized blocks design and related issues

- **Why should prognostic variables be controlled?**

  There are two purposes for controlling prognostic variables:

  (a) To avoid possible confounding of treatment effects with the effects of prognostic variables so as to ensure the credibility of the treatment comparison;

  (b) To better estimate the treatment effects and the error variance so as to increase the power of the test for treatment effects.

  Example: In the breast cancer trial introduced in lecture notes 1, the age of the patients, if uncontrolled, might cause either confounding or imprecision of the comparison.

- **Complete randomized blocks design (CRBD)**

  The design has the following layout of data:

	Treatment					
Block	1	$\cdots$	j	$\cdots$	g	Mean
1	X_{11}	$\cdots$	X_{1j}	$\cdots$	X_{1g}	$\bar{X}_{1\cdot}$
$\vdots$						
i	X_{i1}	$\cdots$	X_{ij}	$\cdots$	X_{ig}	$\bar{X}_{i\cdot}$
$\vdots$						
n	X_{n1}	$\cdots$	X_{nj}	$\cdots$	X_{ng}	$\bar{X}_{n\cdot}$
Mean	$\bar{X}_{\cdot 1}$	$\cdots$	$\bar{X}_{\cdot j}$	$\cdots$	$\bar{X}_{\cdot g}$	$\bar{X}_{\cdot\cdot}$
sd	s_1	$\cdots$	s_j	$\cdots$	s_g	

  The design classifies patients by blocking factors into blocks of size the same as the number of treatments. The treatments are randomly assigned to the patients in each block.

Examples:

In agriculture experiments, different fertilizers are compared by applying them to neighboring plots of land.

In animal experiments, different diets are compared by applying them to the young animals in the same litter.

In clinical trials, patients are matched by enrollment time to avoid possible bias caused by relaxing the eligibility criterion due to some un-foreseeable reasons.

- **Blocking criteria**

Blocking can be done by one factor, e.g., gender, or done by several factors, e.g., gender plus age.

A blocking factor should have potential effects on the end-point measurements.

Blocking criterion should neither be too tight nor too loose. If too tight, it will be hard to recruit enough patients matched in each block. If too loose, the matching will have little effect for controlling prognostic variables.

- **Matched pair design**

Matched pair design is a special case of the CRBD. In a matched pair design, the differences of the measurements of matched pairs are analyzed with the test statistic:

$$\frac{\bar{d}}{\sqrt{\mathrm{Var}(\bar{d})}}, \quad \bar{d} = \frac{1}{n}\sum_{i=1}^{n} d_i,$$

where $d_i = x_{i1} - x_{i2}$.

Had the subjects not been matched, the original measurements are analyzed with the test statistic:

$$\frac{\bar{X}_1 - \bar{X}_2}{\sqrt{\mathrm{Var}(\bar{X}_1 - \bar{X}_2)}}.$$

With matching, we expect a positive correlation ρ between the individual in a pair. Thus

$$\mathrm{Var}(\bar{d}) = \frac{\sigma_1^2 + \sigma_2^2 - 2\rho\sigma_1\sigma_2}{n}.$$

But

$$\mathrm{Var}(\bar{X}_1 - \bar{X}_2) = \frac{\sigma_1^2 + \sigma_2^2}{n}.$$

The reduction of variance in the matched pair design has a positive impact on the power of the test.

Example 1:

In a study to compare Imipramine, an antidepressant drug, with a placebo, 60 patients are paired to form 30 matched blocks. The end-point measurement is the Hamilton rating scale for depression.

Each pair consisted of patients who entered the study within a month of each other, were of the same gender, and were similar in age.

For females, criterion for the matching of age is “less than ten year apart”.

For males, criterion for the matching of age is ”less than 20 years apart”.

Tighter criterion for matching the age would have resulted in many males not being pairable with each other.

The data is summarized below:

	Imi.	Pla.	Diff
Mean	6.3000	7.5667	-1.2667
sd	2.3947	2.5955	2.9235

From the table, it is computed that

$$\mathrm{sd}(\bar{d}) = \frac{2.9235}{\sqrt{30}} = 0.53,$$

$$\mathrm{se}(\bar{X}_1 - \bar{X}_2) = 2.4971\sqrt{\frac{2}{30}} = 0.64,$$

where $2.4971 = \sqrt{(2.3947^2 + 2.5955^2)/2}$
The t-tests based on the differences and the raw measurements have p-values 0.01178 and 0.02627 respectively.

§4.2. Analysis of variance and multiple comparison for CRBD

- **ANOVA table and F-test for treatment effects**

  The usual ANOVA table is valid for the analysis of the CRBD data. The table is as follows:

Source	df	SS	MS	F ratio
Treatments	$g-1$	$n\sum(\bar{X}_{\cdot j}-\bar{X}_{\cdot\cdot})^2$	TMS	$\frac{\text{TMS}}{\text{RMS}}$
Blocks	$n-1$	$g\sum(\bar{X}_{i\cdot}-\bar{X}_{\cdot\cdot})^2$	BMS	
Residuals	$(g-1)(n-1)$	$\sum\sum(X_{ij}-\bar{X}_{i\cdot}-\bar{X}_{\cdot j}+\bar{X}_{\cdot\cdot})^2$	RMS	
Total	$gn-1$	$\sum\sum(X_{ij}-\bar{X}_{\cdot\cdot})^2$		

  Note:

  The error variance is estimated by the residual mean sum of squares (RMS) rather than the usual pooled s^2.

The variation measured by s^2 is a confounded variation caused by both the blocks and the random error.

The residuals can be written as:

$$\begin{aligned} & X_{ij} - \bar{X}_{i\cdot} - \bar{X}_{\cdot j} + \bar{X}_{\cdot\cdot} \\ = \; & (X_{ij} - \bar{X}_{\cdot\cdot}) - (\bar{X}_{i\cdot} - \bar{X}_{\cdot\cdot}) \\ & -(\bar{X}_{\cdot j} - \bar{X}_{\cdot\cdot}). \end{aligned}$$

It is the part of the variation from the total mean after eliminating the effects of the treatments and blocks and hence caused purely by random error. The RMS provides a more accurate estimate of the error variance.

The significance of treatment effects is tested by the F ratio

$$F = \frac{\text{TMS}}{\text{RMS}}.$$

Under the null hypothesis of no treatment effects, the F ratio follows a F-distribution with df $g-1$ and $(g-1)(n-1)$. The significance is claimed at level α if $F > F_{g-1,(g-1)(n-1),\alpha}$.

Example 2. The data:

	Treatment				
Subject	1	2	3	4	Mean
1	8.4	9.4	9.8	12.2	9.950
2	12.8	15.2	12.9	14.4	13.825
3	9.6	9.1	11.2	9.8	9.925
4	9.8	8.8	9.9	12.0	10.125
5	8.4	8.2	8.5	8.5	8.400
6	8.6	9.9	9.8	10.9	9.800
7	8.9	9.0	9.2	10.4	9.375
8	7.9	8.1	8.2	10.0	8.550
Mean	9.300	9.713	9.938	11.025	9.994
sd	1.550	2.294	1.514	1.815	

In the above table, each block represents a different subject, the units within blocks are four blood samples from each subject, and four treatments were randomly assigned to the blood samples within each set. The values are the clotting times of plasm, in minutes.

The ANOVA table is given below:

Source	df	SS	MS	F ratio
Treatments	3	13.0163	4.3388	6.62
Subjects	7	78.9888	11.2841	
Residuals	21	13.7737	0.6559	
Total	31	105.7788		

Note: The pooled s^2 is 3.3128, which is much larger than 0.6559.

The F-test has a p-value

$$1 - P(F_{3,21} > 6.62) = 0.0025.$$

Had the subject effects not been eliminated, a F test with the pooled s^2 as the estimate of the error variance would yield a p-value

$$1 - P(F_{3,28} > 4.3388/3.3128) = 0.29.$$

- **Multiple comparison**

Multiple comparison with CRBD can be carried out similar to that with the parallel groups design. The only modification is to replace WMS (s^2) by RMS. The contrasts are of the form

$$\hat{C} = \sum_{j=1}^{g} c_j \bar{X}_{.j}.$$

Scheffe's criterion: Compare $\frac{\sqrt{n}\hat{C}}{\sqrt{\mathrm{RMS} \sum c_j^2}}$ with $\sqrt{(g-1)F_{g-1,(g-1)(n-1),\alpha}}$.

Tukey's criterion: Compare $\frac{\sqrt{n}|\bar{X}_{\cdot j}-\bar{X}_{\cdot k}|}{\sqrt{\mathrm{RMS}}}$ with $q_{g,(g-1)(n-1),\alpha}$.

Dunnett's criterion: Compare $\frac{\sqrt{n}|\bar{X}_{\cdot j}-\bar{X}_{\text{control}}|}{\sqrt{2\cdot \mathrm{RMS}}}$ with $d_{g-1,(g-1)(n-1),\alpha/2}$.

§4.3. Non-parametric procedures for CRBD

- **Sign test**

The test is for matched pair designs.

Let d_i be the difference of the measurements in the ith pair, n_+ the number of positive differences, and n_- the number of negative differences. Let

$$n_\cdot = n_+ + n_-,$$
$$n_{\max} = \max\{n_+, n_-\}.$$

If the treatments have no different effects, n_+ and n_- should about the same. If any one of them is substantially larger than the other, it is a indication of different treatment effects. Under the null hypothesis of no treatment effects, $n_{\max}$ follows a binomial distribution $\mathrm{Bio}(n., 1/2)$.

The Sign test compares $n_{\max}$ with the binomial distribution. The p-value of the test (two-sided) is computed as

$$p = \frac{2}{2^{n.}} \sum_{i=n_{\max}}^{n.} \binom{n.}{i}.$$

If $n.$ is large (> 10), the Sign test can be based on the statistic

$$Z = \frac{|n_+ - n_-| - 1}{\sqrt{n.}}.$$

It is to be compared with the normal quantile $z_{\alpha/2}$.

- **Wilconxon's signed ranks test**

  The sign test does not take into account the magnitude of the differences. The signed ranks test, which takes into account both the signs as well as the magnitude of the differences, is generally more powerful than the sign test.

  Rank the absolute values of the differences. Let R_+ be the sum of the ranks for the pairs whose differences are positive. The Wilconxon signed ranks test statistic is given by

$$Z = \frac{R_+ - \frac{n.(n.+1)}{4}}{\sqrt{\frac{n.(n.+1)(2n.+1)f}{24}}},$$

  where f is the factor for adjusting ties given in lecture notes 2.

  Under the null hypothesis of no effect difference, the statistic follows a standard normal distribution. The null hypothesis is rejected at level α if $|Z| > z_{\alpha/2}$.

The numerator of Z is equal to

$$\frac{n_+ n_-}{n.}(\bar{R}_+ - \bar{R}_-) + \frac{(n. + 1)(n_+ - n_-)}{4}.$$

This makes it possible for the sign test not to show significance because $n_+ - n_-$ is small, but for the signed ranks test to show significance because $\bar{R}_+ - \bar{R}_-$ might be large.

- **Example 1 (cont.)**

  The original data of the example is given in the table on the next page.

  Sign test: From the table, we obtain $n_+ = 8, n_- = 18$. The Z for the Sign test is

$$Z = \frac{|8 - 18| - 1}{\sqrt{26}} = 1.765,$$

which is less than $z_{0.025} = 1.96$. The null hypothesis of no effect difference is not rejected.

Pair	Imi	Pla	d	Pair	Imi	Pla	d
1	6	4	2	16	6	8	−2
2	4	7	-3	17	10	10	0
3	6	12	-6	18	3	9	-6
4	7	10	-3	19	5	8	-3
5	5	2	3	20	4	5	-1
6	6	11	-5	21	6	8	-2
7	8	9	-1	22	7	7	0
8	7	5	2	23	5	6	-1
9	8	11	-3	24	6	9	-3
10	3	8	-5	25	3	3	0
11	9	7	2	26	10	5	5
12	4	6	-2	27	5	11	-6
13	8	8	0	28	4	7	-3
14	11	9	2	29	4	3	1
15	12	9	3	30	7	10	-3

Signed ranks test: The ranks are given in the following table

Pair	d	$\lvert d \rvert$	Rank	Pair	d	$\lvert d \rvert$	Rank
1	2	2	8	16	-2	2	8
2	-3	3	16	17	0	0	—
3	-6	6	25	18	-6	6	25
4	-3	3	16	19	-3	3	16
5	3	3	16	20	-1	1	2.5
6	-5	5	22	21	-2	2	8
7	-1	1	2.5	22	0	0	—
8	2	2	8	23	-1	1	2.5
9	-3	3	16	24	-3	3	16
10	-5	5	22	25	0	0	—
11	2	2	8	26	5	5	22
12	-2	2	8	27	-6	6	25
13	0	0	—	28	-3	3	16
14	2	2	8	29	1	1	2.5
15	3	3	16	30	-3	3	16

From the table, it is computed that

$$R_+ = 88.5, f = 0.9337, Z = -2.29.$$

Since $|Z| > 1.96$, the test is significant at level $\alpha = 0.05$.

- **Friedman test**

Friedman's test is for the CRBD data with $g > 2$.

The test procedure:

(a) Drop the blocks where all the g measurements are equal, if any.

(b) Rank the g measurements within each of the remaining blocks.

(c) Compute the average ranks $\bar{R}_j, j = 1, \ldots, g$.

(d) Compute the test statistic

$$\chi^2 = \frac{12n.}{g(g+1)} \sum_{j=1}^{g} (\bar{R}_j - \frac{g+1}{2})^2,$$

where $n.$ is the number of blocks in which at least two measurements are unequal.

Under the null hypothesis of no effect difference, the above statistic follows a χ^2-distribution with df $g-1$.

Example 2 (cont.) The Friedman test statistic for this example is computed as follows:

	Measurement				Rank			
Subject	1	2	3	4	1	2	3	4
1	8.4	9.4	9.8	12.2	1	2	3	4
2	12.8	15.2	12.9	14.4	1	4	2	3
3	9.6	9.1	11.2	9.8	2	1	4	3
4	9.8	8.8	9.9	12.0	2	1	3	4
5	8.4	8.2	8.5	8.5	2	1	3.5	3.5
6	8.6	9.9	9.8	10.9	1	3	2	4
7	8.9	9.0	9.2	10.4	1	2	3	4
8	7.9	8.1	8.2	10.0	1	2	3	4
Mean	9.300	9.713	9.938	11.025	1.375	2.000	2.9375	3.6875

$$
\begin{aligned}
\chi^2 &= \frac{12 \times 8}{4 \times 5}[(1.375 - 2.5)^2 + (2 - 2.5)^2 \\
&\quad +(2.9735 - 2.5)^2 + (3.6875 - 2.5)^2] \\
&= 14.96.
\end{aligned}
$$

The p-value is given by

$$P(\chi_3^2 > 14.96) = 0.00185.$$

§4.4. Analysis with missing values

If there are missing values in the CRBD data, the ANOVA method cannot be applied for the analysis.

If values are missing due to reasons related to treatment effects, some ad hoc methods must be considered for the dealing with the missing values.

If values are missing at random, a multiple regression model can be used for the analysis.

• Multiple regression model for CRBD

The data from a CRBD can be described by a general multiple regression model using dummy variables.

Let

$$B_i = \begin{cases} 1 \text{ if in block } & i, \\ 0 \text{ otherwise,} \end{cases}$$

$$i = 1, \ldots, n-1;$$

$$T_j = \begin{cases} 1 \text{ if receives treatment } & j, \\ 0 \text{ otherwise,} \end{cases}$$

$$j = 1, \ldots, g-1.$$

Let $\boldsymbol{y}$ denote the vector with components y_{ij}, i.e.

$$\boldsymbol{y}' = (y_{11}, \ldots, y_{n1}, \ldots, y_{1g}, \ldots, y_{ng}).$$

Let $\boldsymbol{x}_0$ be a vector of components all 1's, $\boldsymbol{t}_j$ the vector of the T_j values of the subjects, $\boldsymbol{b}_i$ the vector of the B_i values of the subjects.

The multiple regression model in matrix form is given by

$$\begin{aligned}\boldsymbol{y} &= \mu_0\boldsymbol{x}_0 + \sum_{i=1}^{n-1}\alpha_i\boldsymbol{b}_i + \sum_{j=1}^{g-1}\beta_j\boldsymbol{b}_j + \boldsymbol{\epsilon}\\ &= \boldsymbol{X}\boldsymbol{\xi} + \boldsymbol{\epsilon},\ \text{say,}\end{aligned}$$

where

$$\begin{aligned}\boldsymbol{X} &= \left[\boldsymbol{x}_0, \boldsymbol{b}_1, \ldots, \boldsymbol{b}_{n-1}, \boldsymbol{t}_1, \ldots, \boldsymbol{t}_{g-1}\right]\\ \boldsymbol{\xi} &= \left(\mu_0, \alpha_1, \ldots, \alpha_{n-1}, \beta_1, \ldots, \beta_{g-1}\right)'.\end{aligned}$$

Interpretation of the parameters:
Let ν_i be the mean value of block i, $i = 1, \ldots, n$. Let μ_j be the mean value of treatment j, $j = 1, \ldots, g$. Then

$$\begin{aligned}\alpha_i &= \nu_i - \nu_n,\ i = 1, \ldots, n-1;\\ \beta_j &= \mu_j - \mu_g,\ j = 1, \ldots, g-1.\end{aligned}$$

- **Some results of the multiple regression model**

Estimation

The least squares method is used to obtained the estimates. The estimate of $\boldsymbol{\xi}$ is given by

$$\hat{\boldsymbol{\xi}} = (\boldsymbol{X}^{'}\boldsymbol{X})^{-1}\boldsymbol{X}^{'}\boldsymbol{y}.$$

The variance-covariance matrix of $\hat{\boldsymbol{\xi}}$ is given by

$$\Sigma = \sigma^2(\boldsymbol{X}^{'}\boldsymbol{X})^{-1},$$

where σ^2 is the error variance. The σ^2 is estimated by the mean residual sum of squares given below:

$$\hat{\sigma}^2 = \frac{\hat{\boldsymbol{\epsilon}}^{'}\hat{\boldsymbol{\epsilon}}}{(n-1)(g-1)},$$

where

$$\hat{\boldsymbol{\epsilon}} = \boldsymbol{y} - \boldsymbol{X}\hat{\boldsymbol{\xi}}.$$

Under the assumption of normality,

$$\hat{\boldsymbol{\xi}} \sim N(\boldsymbol{\xi}, \Sigma).$$

The distribution is asymptotically valid without the normality assumption.

Inference

The hypothesis of no treatment effects is equivalent to

$$\beta_1 = \cdots = \beta_{g-1} = 0.$$

For any contrast C,

$$\sum_{j=1}^{g} c_j \mu_j = \sum_{j=1}^{g-1} c_j \beta_j.$$

Because of the above equivalence, the inference on the overall treatment effects and multiple comparison can be done though the inference on β_j's.

Test for the overall treatment effect:

The Wald test statistic can be used to test the overall treatment effect. Let

$$\hat{\boldsymbol{\beta}} = (\hat{\beta}_1, \ldots, \hat{\beta}_{g-1})',$$

and denote the estimated variance-covariance matrix of $\hat{\boldsymbol{\beta}}$ by $\hat{\Sigma}_\beta$. The statistic is given by

$$\chi^2 = \hat{\boldsymbol{\beta}}' \hat{\Sigma}_\beta^{-1} \hat{\boldsymbol{\beta}}.$$

Under normality assumption,

$$\chi^2 \sim 3 \times F_{g-1,(g-1)(n-1)}.$$

In general, χ^2 has an asymptotic χ^2-distribution with df $g-1$.

Test statistic for contrasts:

Let $\boldsymbol{c} = (c_1, \ldots, c_{g-1})'$. The statistic is given by

$$\hat{C} = \frac{\boldsymbol{c}'\hat{\boldsymbol{\beta}}}{\sqrt{[\boldsymbol{c}'\hat{\Sigma}_\beta \boldsymbol{c}]^{-1}}}.$$

- **Example 2 (cont.)**: Suppose the value for subject 7 treatment 2 is missing.

  The following R-codes are used to generate the response vector and the dummy variable matrix:

```
y1 = c(8.4,12.8,9.6,9.8,8.4,8.6,8.9,7.9)
y2 = c(9.4,15.2,9.1,8.8,8.2,9.9,9.0,8.1)
y3 = c(9.8,12.9,11.2,9.9,8.5,9.8,9.2,8.2)
y4 = c(12.2,14.4,9.8,12.0,8.5,10.9,10.4,10)
y=cbind(y1,y2,y3,y4)
c0=rep(1,32)
e1=e2=e3=e4=e5=e6=e7=rep(0,8)
e1[1]=e2[2]=e3[3]=e4[4]=e5[5]=e6[6]=e7[7]=1
c1=c2=c3=rep(0,32)
c1[1:8]=1
c2[9:16]=1
c3[17:24]=1
b1=rep(e1,4)
b2=rep(e2,4)
b3=rep(e3,4)
b4=rep(e4,4)
b5=rep(e5,4)
b6=rep(e6,4)
b7=rep(e7,4)
X = data.frame(c1,c2,c3,b1,b2,b3,b4,b5,b6,b7)
X=X[-15,]
y=y[-15]
The data matrix is given on the next page.
```

1	8.4	1	0	0	1	0	0	0	0	0	0
2	12.8	1	0	0	0	1	0	0	0	0	0
3	9.6	1	0	0	0	0	1	0	0	0	0
4	9.8	1	0	0	0	0	0	1	0	0	0
5	8.4	1	0	0	0	0	0	0	1	0	0
6	8.6	1	0	0	0	0	0	0	0	1	0
7	8.9	1	0	0	0	0	0	0	0	0	1
8	7.9	1	0	0	0	0	0	0	0	0	0
9	9.4	0	1	0	1	0	0	0	0	0	0
10	15.2	0	1	0	0	1	0	0	0	0	0
11	9.1	0	1	0	0	0	1	0	0	0	0
12	8.8	0	1	0	0	0	0	1	0	0	0
13	8.2	0	1	0	0	0	0	0	1	0	0
14	9.9	0	1	0	0	0	0	0	0	1	0
16	8.1	0	1	0	0	0	0	0	0	0	0
17	9.8	0	0	1	1	0	0	0	0	0	0
18	12.9	0	0	1	0	1	0	0	0	0	0
19	11.2	0	0	1	0	0	1	0	0	0	0
20	9.9	0	0	1	0	0	0	1	0	0	0
21	8.5	0	0	1	0	0	0	0	1	0	0
22	9.8	0	0	1	0	0	0	0	0	1	0
23	9.2	0	0	1	0	0	0	0	0	0	1
24	8.2	0	0	1	0	0	0	0	0	0	0
25	12.2	0	0	0	1	0	0	0	0	0	0
26	14.4	0	0	0	0	1	0	0	0	0	0
27	9.8	0	0	0	0	0	1	0	0	0	0
28	12.0	0	0	0	0	0	0	1	0	0	0
29	8.5	0	0	0	0	0	0	0	1	0	0
30	10.9	0	0	0	0	0	0	0	0	1	0
31	10.4	0	0	0	0	0	0	0	0	0	1
32	10.0	0	0	0	0	0	0	0	0	0	0

The following is the R code and the results:

```
> attach(X)
> lm.fit = lm(y~b1+b2+b3+b4+b5+b6+b7+c1+c2+c3, data=X)
> summary(lm.fit)

Coefficients:
            Estimate Std. Error t value Pr(>|t|)
(Intercept)   9.5768     0.4874  19.650 1.51e-14 ***
b1            1.4000     0.5865   2.387 0.026979 *
b2            5.2750     0.5865   8.994 1.82e-08 ***
b3            1.3750     0.5865   2.344 0.029498 *
b4            1.5750     0.5865   2.685 0.014227 *
b5           -0.1500     0.5865  -0.256 0.800760
b6            1.2500     0.5865   2.131 0.045667 *
b7            0.8607     0.6399   1.345 0.193688
c1           -1.7250     0.4147  -4.159 0.000485 ***
c2           -1.2946     0.4340  -2.983 0.007355 **
c3           -1.0875     0.4147  -2.622 0.016324 *

Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

Residual standard error: 0.8295 on 20 degrees of freedom
Multiple R-Squared: 0.8686,Adjusted R-squared: 0.803
F-statistic: 13.23 on 10 and 20 DF,  p-value: 9.21e-07
```

```
> anova(lm.fit)
Analysis of Variance Table

Response: y
          Df Sum Sq Mean Sq F value    Pr(>F)
b1         1  0.026   0.026  0.0384   0.84670
b2         1 67.376  67.376 97.9282 3.772e-09 ***
b3         1  1.447   1.447  2.1038   0.16244
b4         1  3.763   3.763  5.4699   0.02984 *
b5         1  2.188   2.188  3.1800   0.08973 .
b6         1  1.808   1.808  2.6283   0.12063
b7         1  1.547   1.547  2.2487   0.14935
c1         1  5.443   5.443  7.9114   0.01075 *
c2         1  2.668   2.668  3.8783   0.06293 .
c3         1  4.731   4.731  6.8757   0.01632 *
Residuals 20 13.760   0.688

Signif. codes:  0 *** 0.001 ** 0.01 * 0.05 . 0.1   1

> vv=vcov(lm.fit)
> V=vv[2:4,2:4]
> V= solve(V)
> bb=lm.fit$coef[2:4]
> xx = t(bb)%*%V%*%bb/3
> xx
         [,1]
[1,] 6.221807
```