9. Balanced incomplete block designs (BIBD)

§9.1. The BIBD and its applicable situations in clinical trials

The Design

The BIBD is a block design where the block size k is less than the number of treatments g. The BIBD is balanced in the sense that

1. k treatments are administered in each block;
2. Each treatment appears in the same number of blocks as any of other treatments;
3. Each pair of treatments appear in the same number of blocks as any of other pairs of treatments.

A BIBD with block size k and number of treatment g can be obtained by considering k-tuples of combinations of $1, 2, \ldots, g$.

The following table provides BIBDs for up to six treatments.

$g = 3, k = 2$:	(12), (13), (14)
$g = 4, k = 2$:	(12), (13), (14), (23), (24), (34)
$g = 4, k = 3$:	(123), (124), (134), (234)
$g = 5, k = 2$:	(12), (13), (14), (15), (23), (24), (25), (34), (35), (45)
$g = 5, k = 3$:	(123), (124), (125), (134), (135), (145), (234), (235), (245), (345)
$g = 5, k = 4$:	(1234), (1235), (1245), (1345), (2345)
$g = 6, k = 2$:	(12), (13), (14), (15), (16), (23), (24), (25), (26), (34), (35), (36), (45), (46), (56)
$g = 6, k = 3$:	(123), (124), (136), (145), (156), (235), (246), (256), (345), (346)
$g = 6, k = 4$:	(1234), (1235), (1236), (1245), (1246), (1256), (1345), (1346), (1356), (1456), (2345), (2346), (2356), (2456), (3456)
$g = 6, k = 5$:	(12345), (12346), (12356), (12456), (13456), (23456)

Each of the above designs can be replicated if necessary. For BIBD with treatment up to 28, see Cochran and Cox (1957, pp469-482).

Some properties of BIBD:

r: number of blocks in which any treatment is applied,

λ: number of blocks in which any two treatments are applied,

g, k: as defined previously.

For a BIBD, these numbers satisfy:

$$gr = nk, \ g \leq n, \ \lambda(g-1) = r(k-1).$$

Examples:

1. Five treatments are to be compared in randomized blocks formed by grouping patients who enter the study within no more than tow months, but only two patients are expected to enter the study per month.
2. Six salves for treatment of gum disorder are to be compared in randomized blocks formed by considering each of the mouth's four quadrants.
3. Three methods of injecting an inoculum are to be compared in randomized blocks formed by subject's two arms.

4. For a study of the absorption of different tablets (more than three) to be injected before a meal, the blocks are formed by a subject's three meals per day.

5. Six examiners are to be compared in an interexaminer reliability study by having each patient examined separately and independently by several examiners. each patient define a block, but a patient cannot tolerate more than three examinations.

§9.2. The data analysis for BIBD

- **An example**:

	Examiner						
Patient	1	2	3	4	5	6	Mean
1	10	14	10				11.33
2	3	3		1			2.33
3	7		12			9	9.33
4	3			8	5		5.33
5	20				26	20	22.00
6		20	14		20		18.00
7		5		8		14	9.00
8		14			18	15	15.67
9			12	17	12		13.67
10		18	19			13	16.67
Mean	8.6	11.2	13.2	10.6	16.2	14.2	12.33

The table laid out an interexaminer reliability study where each value is the score on a rating for depression given by the indicated examiner to the indicated patient.

- **The model for BIBD**

  Let X_{ij} be the response value of a subject in block i which received treatment j. Then X_{ij} can be described by

  $$X_{ij} = \mu + s_i + \alpha_j + \epsilon_{ij},$$

  where

  - μ is the overall mean response,
  - s_i is a random effect due to Subject i with mean zero and variance σ_s^2,
  - α_j is the effect due to treatment j subject to $\sum_{j=1}^{g} \alpha_j = 0$,
  - ϵ_{ij}'s are i.i.d. random error with mean zero

and variance σ_ϵ^2 and are independent with s_i's.

- **The analysis of treatment effect**

A naive estimate for α_j is

$$\hat{\alpha}_j = \bar{X}_{\cdot j} - \bar{X}_{\cdot\cdot}.$$

– The naive estimate is unbiased;

– But it is subject to excessive random variation because its variance is affected by both σ_s^2 and σ_ϵ^2.

A intuitively more reasonable estimate is

$$\bar{X}_{\cdot j} - M_j,$$

where M_j is the mean of the responses only in those blocks which involves treatment j.

Let the blocks in which treatment j appears be denoted by j_l, $l = 1, \ldots, r$. Let $\bar{X}_{j_l \cdot}$ be the mean in block j_l. Then

$$M_j = \frac{1}{r} \sum_{l=1}^{r} \bar{X}_{j_l \cdot}$$

and

$$\bar{X}_{\cdot j} - M_j = \frac{1}{r} \sum_{l=1}^{r} (X_{j_l j} - \bar{X}_{j_l \cdot}).$$

It can be derived that

$$E(\bar{X}_{\cdot j} - M_j) = \frac{g(k-1)}{k(g-1)} \alpha_j.$$

Let $\text{EFF} = \frac{g(k-1)}{k(g-1)}$. Then an unbiased estimate of α_j is given by

$$a_j = \frac{1}{\text{EFF}} (\bar{X}_{\cdot j} - M_j).$$

It can be obtained that

$$\mathrm{Var}(a_j) = \frac{g-1}{g}\frac{\sigma_\epsilon^2}{r\mathrm{EFF}}.$$

The sum of squares (the contribution of the treatment effect to the total sum of squares) is then

$$\mathrm{TSS(EB)} \;= r\mathrm{EFF}\sum_{j=1}^{g} a_j^2.$$

The ANOVA table for analyzing treatment effect:

Source	df	SS	MS	E(MS)
Block(IT)	$n-1$	$k\sum(\bar{X}_{i\cdot}-\bar{X}_{\cdot\cdot})^2$	BMS(IT)	$\sigma_\epsilon^2+k\sigma_s^2+\frac{r-\lambda}{k(n-1)}\sum\alpha_j^2$
Tmt(EB)	$g-1$	$r\mathrm{EFF}\sum_{j=1}^{g} a_j^2$	TMS(EB)	$\sigma_\epsilon^2+\frac{r\mathrm{EFF}}{g-1}\sum\alpha_j^2$
Res.	$rg-n-g+1$	By subtraction	RMS	σ_ϵ^2
Total	$rg-1$	$\sum\sum(X_{ij}-\bar{X}_{\cdot\cdot})^2$		

IT: ignoring treatments;

EB: eliminating effects of blocks.

Remark:

By the expected MS of the ANOVA table, it should be noticed that

1. The TMS(EB) does provide a valid measure on the treatment effect;
2. The BMS(IT) does not provide a valid measure on the block effect. In addition, it also measures partially the treatment effect.

The significance of treatment effect is tested by the F ratio:

$$F = \frac{\text{TMS(EB)}}{\text{RMS}}.$$

The value is to be compared with $F_{g-1,rg-n-g+1,\alpha}$ for a test at level α.

Multiple comparison

Multiple comparison is through contrasts of the form

$$C = \sum_{j=1}^{g} c_j a_j, \quad \sum_{j=1}^{g} c_j = 0.$$

The estimated variance of C is

$$\mathrm{Var}(C) = \frac{g-1}{g} \frac{\mathrm{RMS}}{r\mathrm{EFF}} \sum_{j=1}^{g} c_j^2.$$

The test statistic is given by

$$L = \frac{C}{\sqrt{\mathrm{Var}(C)}},$$

which follows a t-distribution with df $rg-n-g+1$.

- **Analysis of block effects**

The sum of squares for blocks ignoring treatments as presented in the ANOVA table in the preceding sub section measures both the block effects and treatment effects in addition to random effects.

A more appropriate sum of squares should measure only the block effects in addition to random effects.

The desired sum of squares for block effects can be obtained in the same way as that for treatment effects.

Note that there is a symmetric structure between blocks and treatments. Mathematically, the treatments can be considered as blocks, and blocks as treatments. When blocks and treatments switch their roles, the following parameters also switch their roles:

$$r \longleftrightarrow k,$$
$$n \longleftrightarrow g,$$

$$\frac{1}{g-1}\sum \alpha_j^2 \longleftrightarrow \sigma_s^2.$$

By using the symmetry above, define

$$\overline{\text{EFF}} = \frac{n(r-1)}{r(n-1)},$$
$$b_i = \frac{1}{\overline{\text{EFF}}}(\bar{X}_{i\cdot} - M_i^{'}),$$

where $M_i^{'}$'s are similarly defined as M_j's.

By the argument of symmetry, we have the following ANOVA table for analyzing block effects:

Source	df	SS	MS	E(MS)
Block(ET)	$n-1$	$k\overline{\text{EFF}}\sum_{i=1}^n b_j^2$	BMS(ET)	$\sigma_\epsilon^2 + k\overline{\text{EFF}}\sigma_s^2$
Tmt(IB)	$g-1$	$r\sum(\bar{X}_{\cdot j}-\bar{X}_{\cdot\cdot})^2$	TMS(IB)	$\sigma_\epsilon^2+\frac{r}{g-1}\sum\alpha_j^2+\frac{g-k}{g-1}\sigma_s^2$
Res.	$rg-n-g+1$	By subtraction	RMS	σ_ϵ^2
Total	$rg-1$	$\sum\sum(X_{ij}-\bar{X}_{\cdot\cdot})^2$		

The significance of block effect is tested by the F ratio:

$$F = \frac{\text{BMS(ET)}}{\text{RMS}}.$$

The value is to be compared with $F_{g-1, rg-n-g+1, \alpha}$ for a test at level α.

The linear model approach

The response X in a BIBD is expressed in another linear model (with reparametrization) as:

$$X = \mu + \sum_{i=2}^{n} \gamma_i b_i + \sum_{j=2}^{g} \beta_j t_j + \epsilon,$$

where

$$b_i = \begin{cases} 1, & \text{if block } i, \\ 0, & \text{otherwise}, \quad i = 2, \ldots, n; \end{cases}$$

$$t_j = \begin{cases} 1, & \text{if treament } j, \\ 0, & \text{otherwise}, \quad j = 2, \ldots, g. \end{cases}$$

Remark:

1. The hypothesis testings for treatment effects and for block effects are equivalent to the testing for $H_0; \beta_2 = \cdots = \beta_g = 0$ and $H_0 : \gamma_2 = \cdots = \gamma_n = 0$, respectively.
2. The multiple comparison on the treatment effects are boiled down to the corresponding linear test on the β parameters.
3. The two ANOVA tables can be obtained by fitting the model twice using the R function `lm`: (a) place the block factor before the treatment factor in the formula specification to get the ANOVA table for inferencing on treatment effects; (b) then place the treatment factor before block factor to get the ANOVA table for inferencing on the block effect.

§9.3. Application to interexaminer reliability study

- **Reliability of measurement**

Measurement reliability concerns with the quality of data: whether or not the data obtained are reliable.

A measurement on a characteristic of a patient can be expressed as

$$X_i = S_i + \epsilon_i,$$

where S_i is the true value of the characteristic which follows a distribution with mean μ and variance σ_s^2, and ϵ_i is a random measurement error distributed with mean zero and variance σ_ϵ^2.

The reliability coefficient is defined as

$$R = \frac{\sigma_s^2}{\sigma_X^2}.$$

In the above simple case, $\sigma_X^2 = \sigma_s^2 + \sigma_\epsilon^2$.

The reliability coefficient reflexes how reliable the measurement is. It should be taken into account if available in sample size calculations.

- **Reliability of the measurements given by different examiners**

Interexaminer reliability arises when measurement of the subjects are taken by different examiners or raters. Suppose the measurement of each subject is taken by a randomly assigned examiner from g examiners. The measurement on subject i taken by examiner j can be expressed as

$$X_{ij} = S_i + \alpha_j + \epsilon_{ij}.$$

In this case,

$$\sigma_X^2 = \sigma_s^2 + \frac{1}{g}\sum_{j=1}^{g} \alpha_j^2 + \sigma_\epsilon^2,$$

and the reliability coefficient is given by

$$R = \frac{\sigma_s^2}{\sigma_s^2 + \frac{1}{g}\sum_{j=1}^{g} \alpha_j^2 + \sigma_\epsilon^2}.$$

- **Estimation of reliability coefficient**

The BIBD can be applied for the interexaminer reliability study to estimate the reliability coefficient. The example presented in the beginning of section 9.2 is in fact an interexaminer reliability study.

Estimate of σ_ϵ^2:

An unbiased estimate of σ_ϵ^2 is given by

$$\hat{\sigma}_\epsilon^2 = \text{RMS}.$$

Estimate of $\nu = \frac{1}{g}\sum_{j=1}^{g}\alpha_j^2$:

From the ANOVA table for inferencing on treatment effects, an unbiased estimate of ν is obtained as

$$\hat{\nu}^2 = \frac{g-1}{r\mathbf{EFF}}\frac{\text{TMS(EB)} - \text{RMS}}{g}.$$

Estimate of σ_s^2:

From the ANOVA table for inferencing on block effects, an unbiased estimate of σ_s^2 is obtained as

$$\hat{\sigma}_s^2 = \frac{1}{k\overline{\mathbf{EFF}}}(\text{BMS(ET)} - \text{RMS}).$$

Estimate of the reliability coefficient

The reliability coefficient R is estimated by

$$R = \frac{\hat{\sigma}_s^2}{\hat{\sigma}_s^2 + \hat{\nu}^2 + \hat{\sigma}_\epsilon^2}.$$

Analysis of the example

The following R code is used for the computation:

```
x=c(10,14,10,3,3,1,7,12,9,3,8,5,20,26,20,20,14,20,
    5,8,14,14,18,15,12,17,12,18,19,13)
examiner = c(1,2,3,1,2,4,1,3,6,1,4,5,1,5,6,
       2,3,5,2,4,6,2,5,6,3,4,5,3,4,6)
examiner = factor(examiner)
patient = factor(kronecker(1:10,c(1,1,1)))
options(contrasts=c("contr.treatment","contr.poly"))
lm.fit1=lm(x~patient+examiner)
anova(lm.fit1)
lm.fit2=lm(x~examiner+patient)
anova(lm.fit2)
```

The computation yield the two ANOVA tables as follows:

For inferencing on treatment (examiner) effects:

```
          Df Sum Sq Mean Sq F value    Pr(>F)    
patient    9 982.00  109.11 11.7558 2.615e-05 ***
examiner   5  35.44    7.09  0.7638    0.5898    
Residuals 15 139.22    9.28                      
```

For inferencing on block (patient) effects:

```
          Df Sum Sq Mean Sq F value    Pr(>F)    
examiner   5 187.07   37.41  4.0310   0.01614 *  
patient    9 830.38   92.26  9.9407 7.267e-05 ***
Residuals 15 139.22    9.28                      
```

It is identified that

$$\begin{aligned} &\mathrm{RMS} = 9.26,\ \mathrm{TMS(EB)} = 7.09, \\ &\mathrm{BMS(ET)} = 92.26. \end{aligned}$$

Computation of $\hat{R}$:

$$\mathrm{EFF} = \frac{6 \times (3-1)}{3 \times (6-1)} = 4/5;$$

$$
\begin{aligned}
\overline{\mathrm{EFF}} &= \frac{10 \times (5-1)}{5 \times (10-1)} = 8/9, \\
\hat{\nu}^2 &= \frac{(6-1)(7.09-9.26)}{6 \cdot 5 \cdot 4/5} = -0.4521, \\
\hat{\sigma}_s^2 &= \frac{1}{3 \cdot 8/9}(92.26-9.26) = 31.125, \\
\hat{R} &= \frac{31.125}{31.125 + (-0.4521) + 9.26} \\
&= 0.7794.
\end{aligned}
$$

§9.4. Combination of BIBD and Latin square designs

A BIBD scheme can be combined with Latin squares in the following way: each block is enlarged to a Latin square. Thus another factor of k (the size of the blocks) levels can be controlled in addition to the block factor.

An example:

The original BIBD scheme:

	Treatment			
Block	1	2	3	4
1	—	—		
2			—	—
3	—		—	
4		—	—	
5	—			—
6		—		—

The enlarged scheme:

	Treatment			
Block	1	2	3	4
1	A	B		
2			B	A
3	B		A	
4		A	B	
5	B			A
6		B		A
7	B	A		
8			A	B
9	A		B	
10		B	A	
11	A			B
12		A		B

The following table provides the data of a study with the enlarged scheme. Four formulations are compared. In addition to the blocks (patients), periods (A, B) are controlled as well. The response is blood level of lithium carbonate (in log units).

	Formulation			
Patient	1	2	3	4
1	-1.0894 (A)	-1.3200 (B)		
2			-1.7577 (B)	-0.9817 (A)
3	-1.0771 (B)		-1.7531 (A)	
4		-0.9381 (A)	-1.6769 (B)	
5	-1.2044 (B)			-0.7795 (A)
6		-1.0395 (B)		-1.0426 (A)
7	-1.0991 (B)	-0.8092 (A)		
8			-2.0245 (A)	-1.3374 (B)
9	-0.9846 (A)		-1.4712 (B)	
10		-1.1395 (B)	-1.6683 (A)	
11	-0.8069 (A)			-1.1913 (B)
12		-0.7789 (A)		-1.1694 (B)

The ANOVA table of the above data is as follows:

Source	df	SS	MS	F
Periods	1	0.1390	0.1390	
Patient (IF)	11	1.1564	0.1051	
Formulation(EP)	3	1.2799	0.4266	18.23
Res.	8	0.1870	0.0234	
Total	23	2.7623		

The following R code can be used for the computation of the ANOVA table (note the order of the factors in the model specification in `lm`):

```
x=c(-1.0894,-1.3200,-1.7577,-0.9817,-1.0771,-1.7531,
       -0.9381,-1.6769,-1.2044,-0.7795,-1.0395,-1.0426,
       -1.0991,-0.8092,-0.7789,-1.1694,-2.0245,-1.3374,
       -0.8069,-1.1913,-0.9846,-1.4712,-1.1395,-1.6683)
patient=kronecker(1:12,c(1,1))
formulation =c(1,2,3,4,1,3,2,3,1,4,2,4,
                         1,2,2,4,3,4,1,4,1,3,2,3)
period = c(1,2,2,1,2,1,1,2,2,1,2,1,
                  2,1,1,2,1,2,1,2,1,2,2,1)
patient = factor(patient)
formulation = factor(formulation)
period = factor(period)
options(contrasts=c("contr.treatment","contr.poly"))
lm.fit=lm(x~period+patient+formulation)
anova(lm.fit)
```

The computation yields the following anova table

	Df	Sum Sq	Mean Sq	F value	Pr(>F)	
period	1	0.13903	0.13903	5.9559	0.0405341	*
patient	11	1.15652	0.10514	4.5039	0.0209792	*
formulation	3	1.27997	0.42666	18.2771	0.0006129	***
Residuals	8	0.18675	0.02334			