Linear and Nonlinear Mixed Effects Models

Yuedong Wang

Department of Statistics and Applied Probability
University of California-Santa Barbara

Classical Random and Mixed Effects Models

Outline

Outline

Outline

Outline

Outline

Outline

Outline

Introduction

This first handout aims to introduce some classical random and mixed effects ANOVA models. It helps to understand the logic behind random effects. I will concentrate on models and classical inference methods in this handout. I will discuss the shortcomings of classical approaches that motivate the likelihood-based approaches we will learn in this class.

Introduction

ANOVA is often used to investigate the effect of a factor or combinations of factors, usually for designed experiments. In 220A, we have learned one-way and two-way ANOVA models. The following concepts are important when constructing an ANOVA model.

- `Experiment unit` (EU): the item to which a factor level is assigned
- `Treatment structure`: sets of factors one wants to compare
- `Design structure`: how experiment units are assigned to factors

Introduction

ANOVA is often used to investigate the effect of a factor or combinations of factors, usually for designed experiments. In 220A, we have learned one-way and two-way ANOVA models. The following concepts are important when constructing an ANOVA model.

- `Experiment unit` (EU): the item to which a factor level is assigned
- `Treatment structure`: sets of factors one wants to compare
- `Design structure`: how experiment units are assigned to factors

Introduction

ANOVA is often used to investigate the effect of a factor or combinations of factors, usually for designed experiments. In 220A, we have learned one-way and two-way ANOVA models. The following concepts are important when constructing an ANOVA model.

- `Experiment unit` (EU): the item to which a factor level is assigned
- `Treatment structure`: sets of factors one wants to compare
- `Design structure`: how experiment units are assigned to factors

Personnel example

A company wants to compare ratings given by its 5 personnel `officers` to potential employees. Four prospective employees were assigned at random to each of 5 officers. The response is `rate`.

- EU: a candidate
- Treatment structure: one-way layout (`officer`)
- Design structure: completely randomized design

Personnel example

A company wants to compare ratings given by its 5 personnel `officers` to potential employees. Four prospective employees were assigned at random to each of 5 officers. The response is `rate`.

- EU: a candidate
- Treatment structure: one-way layout (`officer`)
- Design structure: completely randomized design

Personnel example

A company wants to compare ratings given by its 5 personnel `officers` to potential employees. Four prospective employees were assigned at random to each of 5 officers. The response is `rate`.

- EU: a candidate
- Treatment structure: one-way layout (`officer`)
- Design structure: completely randomized design

Personnel example

Observations are listed in the following table.

Officer	Candidate			
	1	2	3	4
A	76	64	85	75
B	58	75	81	66
C	49	63	62	46
D	74	71	85	90
E	66	74	81	79

Goal: investigate if there are significant differences between officers.

One-way ANOVA Model

For the personnel example, the following one-way ANOVA model is often assumed

$$y_{ij} = \mu + \alpha_i + \epsilon_{ij}$$

- i: level index, $i = 1, \cdots, a$
  j: observation index, $j = 1, \cdots, n_i$
- y_{ij}: jth observation at level i
- μ: overall mean
- α_i: effect at level i, $\sum_{i=1}^{a} \alpha_i = 0$
- ϵ_{ij}: random errors

Random effect

Now suppose that 5 officers were *randomly selected* from all (more than 5) personnel officers and, rather than among the 5 selected officers, the company wanted to investigate differences among *all personnel officers in the company*.

Key characteristics

- The levels of the factor are chosen *at random* from a well-defined population of factor levels
- Draw inference about the *general population* using information from these observed (chosen) levels

Random effect

Now suppose that 5 officers were *randomly selected* from all (more than 5) personnel officers and, rather than among the 5 selected officers, the company wanted to investigate differences among *all personnel officers in the company*.

Key characteristics

- The levels of the factor are chosen *at random* from a well-defined population of factor levels
- Draw inference about the *general population* using information from these observed (chosen) levels

Conditional expected response

In general, suppose that we have one factor (e.g., `officer`). For a randomly selected level (e.g., an officer) U from the population of all levels (e.g., all officers in the company), define

$$\mathrm{E}(y|U) = M(U).$$

Note that $M(U)$ is a random variable since U is a random variable. We assume that

$$M(U) \sim \mathrm{N}(\mu, \sigma_a^2),$$

where

- μ: population mean for all levels
- σ_a^2: variance between levels

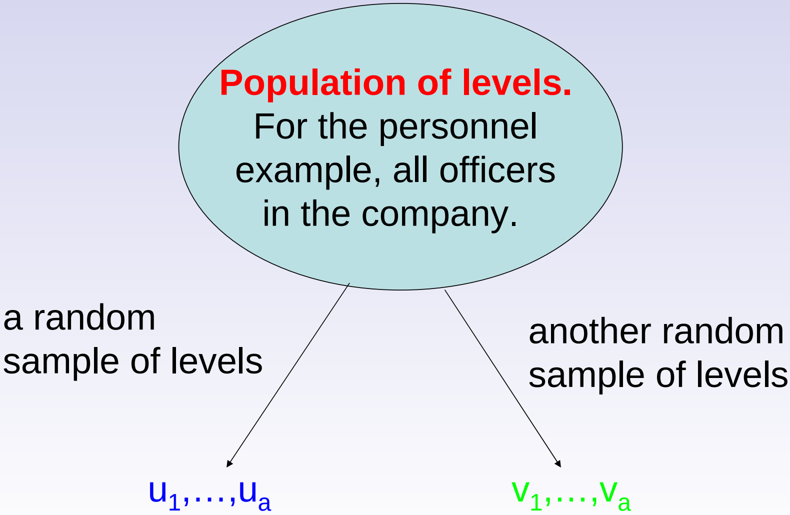
Conditional expected responses for selected levels

Denote $u_1, \cdots, u_a$ as a selected levels (or realizations of U) and

$$M_i = M(u_i), \quad i = 1, \cdots, a,$$

as the conditional expected responses. Note that for a different sample of levels, the conditional expected responses would be different, which reflects variation between levels.

Population and samples of levels



One-way random effects model

The one-way random effects model assumes that

$$y_{ij} = M_i + \epsilon_{ij}$$

- i: level index, $i = 1, \cdots, a$
  j: observation index, $j = 1, \cdots, n_i$
- y_{ij}: jth observation at level u_i
- M_i: conditional expected response at level u_i,
  $M_i \overset{iid}{\sim} N(\mu, \sigma_a^2)$
- ϵ_{ij}: random errors, $\epsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2)$
- M_i and ϵ_{ij} are mutually independent

One-way random effects model

The one-way random effects model can be written in the effect form as

$$y_{ij} = \mu + \alpha_i + \epsilon_{ij}$$

- μ: overall mean
- α_i: effect at level i, $\alpha_i \overset{iid}{\sim} N(0, \sigma_a^2)$. Similar to the sum-to-zero condition for a one-way fixed effects model, the condition that $E(\alpha_i) = 0$ makes the model identifiable.
- ϵ_{ij}: random errors, $\epsilon_{ij} \overset{iid}{\sim} N(0, \sigma^2)$
- α_i and ϵ_{ij} are mutually independent

Properties of the one-way random effects model

- $E(y_{ij}) = \mu$, a constant representing the mean of the population
- $\text{Var}(y_{ij}) = \sigma_a^2 + \sigma^2$. There are two sources of variations: variation *between* levels σ_a^2 and variation *within* levels σ^2
- $$\text{Cov}(y_{i_1,j_1}, y_{i_2,j_2}) = \begin{cases} \sigma_a^2 & i_1 = i_2, \\ 0 & i_1 \neq i_2. \end{cases}$$

  Thus observations within the same level are *correlated*. This fact provides a way to model the correlation structure.
- $\text{corr}(y_{i,j_1}, y_{i,j_2}) = \sigma_a^2/(\sigma_a^2 + \sigma^2)$ is called the intraclass correlation coefficient (ICC). It represents the proportion of the total variation accounted for by the factor.

Properties of the one-way random effects model

- $\mathrm{E}(y_{ij}) = \mu$, a constant representing the mean of the population
- $\mathrm{Var}(y_{ij}) = \sigma_a^2 + \sigma^2$. There are two sources of variations: variation *between* levels σ_a^2 and variation *within* levels σ^2
- $$\mathrm{Cov}(y_{i_1,j_1}, y_{i_2,j_2}) = \begin{cases} \sigma_a^2 & i_1 = i_2, \\ 0 & i_1 \neq i_2. \end{cases}$$
  Thus observations within the same level are *correlated*. This fact provides a way to model the correlation structure.
- $\mathrm{corr}(y_{i,j_1}, y_{i,j_2}) = \sigma_a^2/(\sigma_a^2 + \sigma^2)$ is called the intraclass correlation coefficient (ICC). It represents the proportion of the total variation accounted for by the factor.

Properties of the one-way random effects model

- $E(y_{ij}) = \mu$, a constant representing the mean of the population
- $\mathrm{Var}(y_{ij}) = \sigma_a^2 + \sigma^2$. There are two sources of variations: variation *between* levels σ_a^2 and variation *within* levels σ^2
- $$\mathrm{Cov}(y_{i_1,j_1}, y_{i_2,j_2}) = \begin{cases} \sigma_a^2 & i_1 = i_2, \\ 0 & i_1 \neq i_2. \end{cases}$$

  Thus observations within the same level are *correlated*. This fact provides a way to model the correlation structure.
- $\mathrm{corr}(y_{i,j_1}, y_{i,j_2}) = \sigma_a^2/(\sigma_a^2 + \sigma^2)$ is called the intraclass correlation coefficient (ICC). It represents the proportion of the total variation accounted for by the factor.

Properties of the one-way random effects model

- $E(y_{ij}) = \mu$, a constant representing the mean of the population
- $\text{Var}(y_{ij}) = \sigma_a^2 + \sigma^2$. There are two sources of variations: variation *between* levels σ_a^2 and variation *within* levels σ^2
- $$\text{Cov}(y_{i_1,j_1}, y_{i_2,j_2}) = \begin{cases} \sigma_a^2 & i_1 = i_2, \\ 0 & i_1 \neq i_2. \end{cases}$$

  Thus observations within the same level are *correlated*. This fact provides a way to model the correlation structure.
- $\text{corr}(y_{i,j_1}, y_{i,j_2}) = \sigma_a^2/(\sigma_a^2 + \sigma^2)$ is called the intraclass correlation coefficient (ICC). It represents the proportion of the total variation accounted for by the factor.

ANOVA table and hypothesis

Source	df	SS	MS	F
Factor	$a-1$	SSA	MSA	MSA/MSE
Error	$\sum n_i - a$	SSE	MSE	
Total	$\sum n_i - 1$	SST		

SSA, SSE, MSA and MSE are the same as those in one-way fixed effects models. However, the hypothesis of interest now is

$$H_0 : \ \sigma_a^2 = 0 \quad \text{vs} \quad H_1 : \ \sigma_a^2 > 0$$

Note that the hypothesis is about the variance parameter rather than the mean parameters. It is different from the usual hypothesis in a one-way fixed effects model.

F test

It can be shown (assignment) that

$$\begin{aligned} E(MSA) &= \sigma^2 + n_0\sigma_a^2 \\ E(MSE) &= \sigma^2 \end{aligned}$$

where

$$n_0 = \frac{n - \sum_{i=1}^a n_i^2/n}{a-1}, \quad n = \sum_{i=1}^a n_i.$$

$E(MSA) = E(MSE)$ under H_0. Thus a large ratio MSA/MSE provides evidence against H_0. Formally, we reject H_0 when the F statistic

$$F = \frac{MSA}{MSE} \overset{H_0}{\sim} F_{a-1,n-a}$$

exceeds a critical value. Note that the F test is the same as the one-way fixed effects model. However, the hypothesis is different.

Estimation

An unbiased estimate of μ is

$$\hat{\mu} = \bar{y}_{..} \triangleq \frac{\sum_{i=1}^{a} \sum_{j=1}^{n_i} y_{ij}}{\sum_{i=1}^{a} n_i}$$

Since $\mathrm{E}(MSE) = \sigma^2$, an unbiased estimate of σ^2 is

$$\hat{\sigma}^2 = MSE$$

Since $\mathrm{E}(MSA) = \sigma^2 + n_0\sigma_a^2$, an unbiased estimate of σ_a^2 is

$$\hat{\sigma}_a^2 = (MSA - MSE)/n_0$$

Plugging-in estimates of $\hat{\sigma}^2$ and $\hat{\sigma}_a^2$, we get an estimate of ICC. Above are moment estimates of parameters. We can also use MLE or REML (restricted maximum likelihood).

Software

There are several SAS procedures and R functions that deal with random and mixed effects models.

SAS

- `proc glm`: fit a general linear model which allows random effects
- `proc varcomp`: estimate variance components for a general linear model
- `proc mixed`: fit a general linear mixed effects model

R

- `aov`: fit an analysis of variance model
- `lme` in the `nlme` library: fit a general linear mixed effects model for nested grouping factors for the random effects.
- `lme4`: fit a general linear mixed effects model for nested or crossed grouping factors for the random effects.

We include the classical ANOVA approach implemented in `proc glm` and `proc varcomp` in this handout only.

SAS procedures proc glm

PROC GLM *<options>*;
CLASS *variables*;
MODEL *dependents=independents </ options>*;
RANDOM *effects </options>*;
CONTRAST *'label' effects values <...effects values></options>*;
ESTIMATE *'label' effects values <...effects values></options>*;
LSMEANS *effects</options>*;
MEANS *effects</options>*;
TEST < **H**=*effects* > **E** *effects</options>*;

SAS analysis of the personnel data

Input data

```
options nocenter ps=64 ls=76;
data a;
   input officer $ @;
   do cand=1 to 4;
     input rate @;
     output;
   end;
   cards;
   A 76 64 85 75
   B 58 75 81 66
   C 49 63 62 46
   D 74 71 85 90
   E 66 74 81 79
   ;
```

SAS analysis of the personnel data

ANOVA

```
proc glm;
   class officer;
   model rate = officer / ss1;
   random officer / test;
```

SAS output of the personnel data

```
Class Level Information
Class     Levels    Values
OFFICER        5    A B C D E
Number of observations in data set = 20

General Linear Models Procedure
Dependent Variable: RATE
                        Sum of     Mean
Source             DF   Squares    Square   F Value   Pr > F
Model               4   1480.00    370.00    4.89     0.0100
Error              15   1134.00     75.60
Corrected Total    19   2614.00

                  R-Square   C.V.      Root MSE   RATE Mean
                  0.566182  12.24623   8.69483     71.0000

Source             DF   Type I SS   Mean Square   F Value   Pr > F
OFFICER             4    1480.00      370.00        4.89     0.0100
```

Conclusion: Ratings from different officers are significantly different with p-value=.01.

SAS analysis of the personnel data

Estimate variance components

```
proc varcomp method=type1;
   class officer;
   model rate = officer;
```

SAS output of the personnel data

```
Variance Components Estimation Procedure
Dependent Variable: RATE
Source                    DF        Type I SS           Type I MS
OFFICER                    4    1480.00000000      370.00000000
Error                     15    1134.00000000       75.60000000
Corrected Total           19    2614.00000000

Source                    Expected Mean Square
OFFICER                   Var(Error) + 4 Var(OFFICER)
Error                     Var(Error)

Variance Component                   Estimate
Var(OFFICER)                      73.60000000
Var(Error)                        75.60000000
```

$$\hat{\sigma}_a^2 = 73.6, \quad \hat{\sigma}^2 = 75.6$$

Spectrophotometer example

A manufacture was developing a new spectrophotometer for use in medical clinical laboratories.

Question: a critical component of instrument performance is the consistency of measurement from day to day among machines. More precisely, the investigators wanted to know if the variability of measurements among machines operated over several days was within acceptable standards for clinical applications.

Treatment structure: a factorial design with 4 levels for each of the two factors: `machine` and `day`.

Spectrophotometer example

Design structure: 4 machines were randomly selected from the pilot assembly production. 8 replicate serum samples were prepared each day from the same stock reagents. 2 serum samples were randomly assigned to each of the 4 machines on each of the 4 randomly selected days. Therefore, we have a completely randomized design with 2 replications of each treatment and day combination. The same technician prepared the serum samples and operated the machines throughout the experiment.

Both `machine` and `day` factors are random since they are selected at random from populations of machines and days on which the machines could be run.

Spectrophotometer example

The observations on triglyceride levels (mg/dl) in the serum samples are shown in the following table.

Day	Machine			
	1	2	3	4
1	142.3, 144.0	148.6, 146.9	142.9, 147.4	133.8, 133.2
2	134.9, 146.3	145.2, 146.3	125.9, 127.6	108.9, 107.5
3	148.6, 156.5	148.6, 153.1	135.5, 138.9	132.1, 149.7
4	152.0, 151.4	149.7, 152.0	142.9, 142.3	141.7, 141.2

Conditional expected responses for selected levels

In general, suppose that we have two factors: A and B (e.g., `machine` and `day`). For a randomly selected level (e.g., a machine) U from the population of all levels for the factor A, and a randomly selected level (e.g., a day) W from the population of all levels for the factor B, define

$$\mathrm{E}(y|U, W) = M(U, W).$$

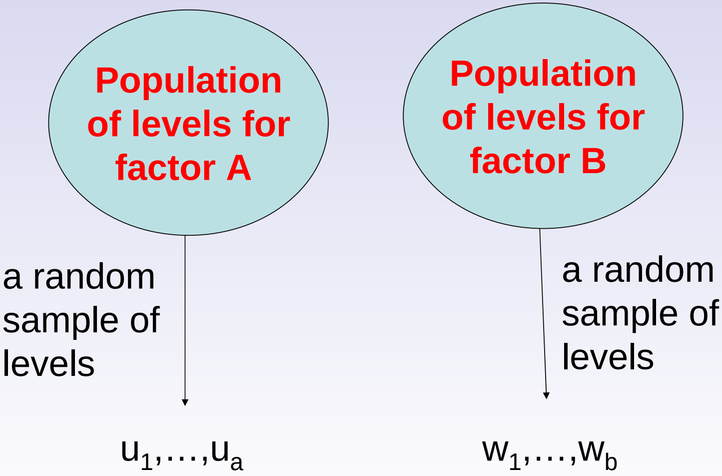
Note that $M(U, W)$ is a random variable since U and W are random variables. We assume that

$$M(U, W) \sim \mathrm{N}(\mu, \sigma^2_{all}),$$

where

- μ: population mean for all combinations of levels
- σ^2_{all}: variance between all combinations of levels

Population and samples of levels



Conditional expected response

Denote $u_1, \cdots, u_a$ as a selected levels (or realizations of U) for factor A, $w_1, \cdots, w_b$ as b selected levels for factor B, and

$$M_{ij} = M(u_i, w_j), \quad i = 1, \cdots, a, \; j = 1, \cdots, b,$$

as the conditional expected responses. Note that for a different sample of levels, the conditional expected responses would be different, which reflects variation between levels.

Two-way random effects model

The two-way random effects model assumes that

$$y_{ijk} = M_{ij} + \epsilon_{ijk}.$$

- i: level index of factor A, $i = 1, \cdots, a$
  j: level index of factor B, $j = 1, \cdots, b$
  k: observation index, $k = 1, \cdots, n_{ij}$
- y_{ijk}: kth observation at level u_i of factor A and level w_j of factor B
- M_{ij}: conditional expected response at level u_i of factor A and level w_j of factor B. $M_{ij} \overset{iid}{\sim} N(\mu, \sigma^2_{all})$
- ϵ_{ijk}: random errors, $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$
- M_{ij} and ϵ_{ijk} are independent of each other

Two-way random effects model

The two-way random effects model can be written in the effect form as

$$y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \epsilon_{ijk}$$

- μ: overall mean
- α_i, β_j and $(\alpha\beta)_{ij}$: main effects of factor A, main effects of factor B, and interaction between A and B
- $\alpha_i \overset{iid}{\sim} N(0, \sigma_a^2)$
  $\beta_j \overset{iid}{\sim} N(0, \sigma_b^2)$
  $(\alpha\beta)_{ij} \overset{iid}{\sim} N(0, \sigma_{ab}^2)$
- ϵ_{ijk}: random errors, $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$
- α_i, β_j, $(\alpha\beta)_{ij}$ and ϵ_{ijk} are mutually independent
- $\sigma_{all}^2 = \sigma_a^2 + \sigma_b^2 + \sigma_{ab}^2$

ANOVA table

For balanced designs with $n = n_{ij}$, we have

Source	df	SS	MS	E(MS)	F
A	$a-1$	SSA	MSA	$\sigma^2 + n\sigma_{ab}^2 + nb\sigma_a^2$	MSA/MSAB
B	$b-1$	SSB	MSB	$\sigma^2 + n\sigma_{ab}^2 + na\sigma_b^2$	MSB/MSAB
AB	$(a-1)(b-1)$	SSAB	MSAB	$\sigma^2 + n\sigma_{ab}^2$	MSAB/MSE
error	$ab(n-1)$	SSE	MSE	σ^2	
Total	$abn-1$	SST			

SSA, SSB, SSAB, MSA, MSB, MSAB, SSE and MSE are the same as those in two-way fixed effects models. We construct F statistics as follows.

$$\begin{aligned} \mathrm{H}_0 &: \sigma_{ab}^2 = 0, \quad F = MSAB/MSE \\ \mathrm{H}_0 &: \sigma_a^2 = 0, \quad F = MSA/MSAB \\ \mathrm{H}_0 &: \sigma_b^2 = 0, \quad F = MSB/MSAB \end{aligned}$$

SAS analysis of the spectrophotometer data

Input data

```
data a;
   do machine=1 to 4;
      do day=1 to 4;
         do rep=1 to 2;
            input y @;
            output;
         end;
      end;
   end;
   cards;
142.3 144.0
134.9 146.3
148.6 156.5
152.0 151.4
148.6 146.9
145.2 146.3
148.6 153.1
149.7 152.0
142.9 147.4
125.9 127.6
135.5 138.9
142.9 142.3
133.8 133.2
108.9 107.5
132.1 149.7
141.7 141.2
   ;
```

SAS analysis of the spectrophotometer data

```
proc glm;
   class day machine;
   model y = day | machine ;
   random day | machine / test;

proc varcomp method=type1;
   class day machine;
   model y = day | machine ;
```

SAS analysis of the spectrophotometer data

```
General Linear Models Procedure
Class Level Information
Class     Levels    Values
DAY            4    1 2 3 4
MACHINE        4    1 2 3 4
Number of observations in data set = 32
```

```
General Linear Models Procedure
Dependent Variable: Y
                          Sum of          Mean
Source           DF      Squares        Square  F Value   Pr > F
Model            15   3767.77719     251.18515    14.04   0.0001
Error            16    286.32500      17.89531
Corrected Total  31   4054.10219

              R-Square        C.V.      Root MSE       Y Mean
              0.929374    2.996284       4.23029      141.184

Source              DF    Type I SS   Mean Square F Value   Pr > F
DAY                  3   1334.46344     444.82115   24.86   0.0001
MACHINE              3   1647.27844     549.09281   30.68   0.0001
DAY*MACHINE          9    786.03531      87.33726   4.88    0.0029

Source              DF Type III SS   Mean Square  F Value Pr > F
DAY                  3  1334.46344     444.82115   24.86   0.0001
MACHINE              3  1647.27844     549.09281   30.68   0.0001
DAY*MACHINE          9   786.03531      87.33726    4.88   0.0029
```

SAS analysis of the spectrophotometer data

```
General Linear Models Procedure
Source          Type III Expected Mean Square
DAY             Var(Error) + 2 Var(DAY*MACHINE) + 8 Var(DAY)
MACHINE         Var(Error) + 2 Var(DAY*MACHINE) + 8 Var(MACHINE)
DAY*MACHINE     Var(Error) + 2 Var(DAY*MACHINE)

General Linear Models Procedure
Tests of Hypotheses for Random Model Analysis of Variance
Dependent Variable: Y
Source: DAY
Error: MS(DAY*MACHINE)
                        Denominator  Denominator
    DF    Type III MS            DF           MS    F Value Pr > F
     3   444.82114583             9  87.337256944   5.0931  0.0248
Source: MACHINE
Error: MS(DAY*MACHINE)
                        Denominator  Denominator
    DF    Type III MS            DF             MS  F Value Pr > F
     3    549.0928125             9   87.337256944  6.2870  0.0137
Source: DAY*MACHINE
Error: MS(Error)
                        Denominator  Denominator
    DF    Type III MS            DF           MS    F Value Pr > F
     9   87.337256944            16   17.8953125    4.8805  0.0029
```

SAS analysis of the spectrophotometer data

```
Variance Components Estimation Procedure
Dependent Variable: Y
Source              DF        Type I SS          Type I MS
DAY                  3    1334.46343750       444.82114583
MACHINE              3    1647.27843750       549.09281250
DAY*MACHINE          9     786.03531250        87.33725694
Error               16     286.32500000        17.89531250
Corrected Total     31    4054.10218750

Source              Expected Mean Square
DAY                 Var(Error) + 2 Var(DAY*MACHINE) + 8 Var(DAY)
MACHINE             Var(Error) + 2 Var(DAY*MACHINE) + 8 Var(MACHINE)
DAY*MACHINE         Var(Error) + 2 Var(DAY*MACHINE)
Error               Var(Error)

Variance Componen               Estimate
Var(DAY)                     44.68548611
Var(MACHINE)                 57.71944444
Var(DAY*MACHINE)             34.72097222
Var(Error)                   17.89531250
```

Unbalanced design

For unbalanced designs, we may use combinations of mean squares in the denominator and Satterthwaite method to approximate the degrees of freedom and distributions.
A (better) more direct approach is to fit a general linear mixed effects model using `proc mixed` or `lme`.

Satterthwaite approximation

The weighted sum of independent χ^2 random variables is rather messy. In practice, a rough approximation can be obtained. Suppose that we have

$$S = \sum w_i \hat{\sigma}_i^2,$$

and would like to approximate S by a χ^2 random variable, up to a constant. One approach (Satterthwaite method) is to match the first two moments. Specifically, we want to find a constant a and a degree of freedom r, such that S and a random variable $X/a \sim \chi^2_r$ have the same first two moments. This leads to

$$\mathrm{E}(S) = ar \quad \text{and} \quad \mathrm{V}(S) = 2a^2 r.$$

Solve the above equations, we have

$$\begin{aligned} r &= 2[\mathrm{E}(S)]^2 / V(S) \\ a &= \mathrm{E}(S)/r = V(S)/2\mathrm{E}(S). \end{aligned}$$

Satterthwaite approximation

- Typically, r is not an integer.
- It is a general method.
- It is quick and easy.
- The performance can be quite poor.
- Welch's t test:

$$S = \hat{\sigma}_1^2/n_1 + \hat{\sigma}_2^2/n_2$$

The approximate degree of freedom

$$r = \frac{(\sigma_1^2/n_1 + \sigma_2^2/n_2)^2}{\sigma_1^4/n_1^2(n_1 - 1) + \sigma_2^4/n_2^2(n_2 - 1)}.$$

SAS analysis of the spectrophotometer data - unbalanced

For illustration, we delete the first observation which makes the design unbalanced.

```
data b;
   set a;
   if _N_=1 then delete;

proc glm;
   class day machine;
   model y = day | machine ;
   random day | machine / test;

proc varcomp method=type1;
   class day machine;
   model y = day | machine ;
```

SAS analysis of the spectrophotometer data - unbalanced

```
The GLM Procedure
    Class Level Information
Class          Levels    Values
day                 4    1 2 3 4
machine             4    1 2 3 4
Number of Observations Read          31
Number of Observations Used          31

The GLM Procedure
Dependent Variable: y
                                   Sum of
Source            DF       Squares  Mean Square F Value  Pr > F
Model             15   3767.937419   251.195828   13.23  <.0001
Error             15    284.880000    18.992000
Corrected Total   30   4052.817419
```

SAS analysis of the spectrophotometer data - unbalanced

R-Square	Coeff Var	Root MSE	y Mean
0.929708	3.087518	4.357981	141.1484

Source	DF	Type I SS	Mean Square	F Value	Pr > F
day	3	1333.187419	444.395806	23.40	<.0001
machine	3	1691.873700	563.957900	29.69	<.0001
day*machine	9	742.876300	82.541811	4.35	0.0061

Source	DF	Type III SS	Mean Square	F Value	Pr > F
day	3	1335.698421	445.232807	23.44	<.0001
machine	3	1607.195132	535.731711	28.21	<.0001
day*machine	9	742.876300	82.541811	4.35	0.0061

SAS analysis of the spectrophotometer data - unbalanced

```
Source       Type III Expected Mean Square
day          Var(Error) + 1.8947 Var(day*machine) +
             7.5789 Var(day)
machine      Var(Error) + 1.8947 Var(day*machine) +
             7.5789Var(machine)
day*machine Var(Error) + 1.92 Var(day*machine)

Tests of Hypotheses for Random Model Analysis of Variance
Dependent Variable: y
Source       DF Type III SS Mean Square F Value Pr > F
day           3 1335.698421  445.232807    5.45 0.0204
machine       3 1607.195132  535.731711    6.56 0.0120
Error    9.0553    739.865312     81.705629
Error: 0.9868*MS(day*machine) + 0.0132*MS(Error)

Source            DF Type III SS Mean Square F Value Pr > F
day*machine        9  742.876300   82.541811    4.35 0.0061
Error: MS(Error)  15  284.880000   18.992000
```

SAS analysis of the spectrophotometer data - unbalanced

Why the combination of mean squares

0.9868*MS(day*machine) + 0.0132*MS(Error)

is used for testing day and machine main effects?

$$
\begin{aligned}
& \text{E (0.9868*MS(day*machine) + 0.0132*MS(Error))} \\
= \; & \text{E(MS(Error)) + 0.9868*(MS(day*machine)-MS(Error))} \\
= \; & \text{Var(Error) + 0.9868*1.92 Var(day*machine)} \\
= \; & \text{Var(Error) + 1.8947 Var(day*machine)}
\end{aligned}
$$

SAS analysis of the spectrophotometer data - unbalanced

Type 1 Analysis of Variance

Source	DF	Sum of Squares	Mean Square
day	3	1333.187419	444.395806
machine	3	1691.873700	563.957900
day*machine	9	742.876300	82.541811
Error	15	284.880000	18.992000
Corrected Total	30	4052.817419	.

SAS analysis of the spectrophotometer data - unbalanced

```
                         Type 1 Analysis of Variance
Source               Expected Mean Square
day                  Var(Error) + 1.9631 Var(day*machine) +
                     0.0276 Var(machine) + 7.7419 Var(day)
machine              Var(Error) + 1.9543 Var(day*machine) +
                     7.7143 Var(machine)
day*machine          Var(Error) + 1.92 Var(day*machine)
Error                Var(Error)
Corrected Total      .
          Type 1 Estimates
Variance Component        Estimate
Var(day)                  46.33271
Var(machine)              62.25868
Var(day*machine)          33.09886
Var(Error)                18.99200
```

Machine example

A company wanted to replace the machines used to make a certain component. Three different brands of `machines` were available, so the investigators designed an experiment to evaluate the productivity of the machines when operated by the company's own personnel. 6 `workers` were randomly selected to participate in the experiment, each of whom was to operate each machine 3 different times. The response is an overall productivity `score`.

Goal: to investigate effects of `machine` and `worker` on the score. There are two factors:

- `machine` is considered as fixed with 3 levels (3 brands are all available or all the company was interested in)
- `worker` is considered random since they were randomly selected from all employees, and the company is interested in the productivity of these machines for all employees rather then the selected 6 employees

Machine data

		Score					
Machine	Person	All scores-Balanced			Partial scores-Unbalanced		
1	1	52.0	52.8	53.1	52.0		
1	2	51.8	52.8	53.1	51.8	52.8	
1	3	60.0	60.2	58.4	60.0		
1	4	51.1	52.3	50.3	51.1	52.3	
1	5	50.9	51.8	51.4	50.9	51.8	51.4
1	6	46.4	44.8	49.2	46.4	44.8	49.2
2	1	62.1	62.6	64.0			64.0
2	2	59.7	60.0	59.0	59.7	60.0	59.0
2	3	68.6	65.8	69.7	68.6	65.8	
2	4	63.2	62.8	62.2	63.2	62.8	62.2
2	5	64.8	65.0	65.4	64.8	65.0	
2	6	43.7	44.2	43.0	43.7	44.2	43.0
3	1	67.5	67.2	66.9	67.5	67.2	66.9
3	2	61.5	61.7	62.3	61.5	61.7	62.3
3	3	70.8	70.6	71.0	70.8	70.6	71.0
3	4	64.1	66.2	64.0	64.1	66.2	64.0
3	5	72.1	72.0	71.1	72.1	72.0	71.1
3	6	62.0	61.4	60.5	62.0	61.4	60.5

Conditional expected response

In general, suppose that we have two factors with one fixed and one random. Denote two factors as factors A and B with a and b levels, respectively. Suppose that factor A is fixed (e.g., machine) and factor B is random (e.g., worker).
For level i of factor A, and a randomly selected level W from the population of all levels for factor B, define

$$\mathrm{E}(y|i, W) = M(i, W).$$

Note that i is deterministic. Nevertheless, $M(i, W)$ is a random variable since W is a random variable. We assume that

$$M(i, W) \sim \mathrm{N}(\mu_i, \sigma^2_{all}).$$

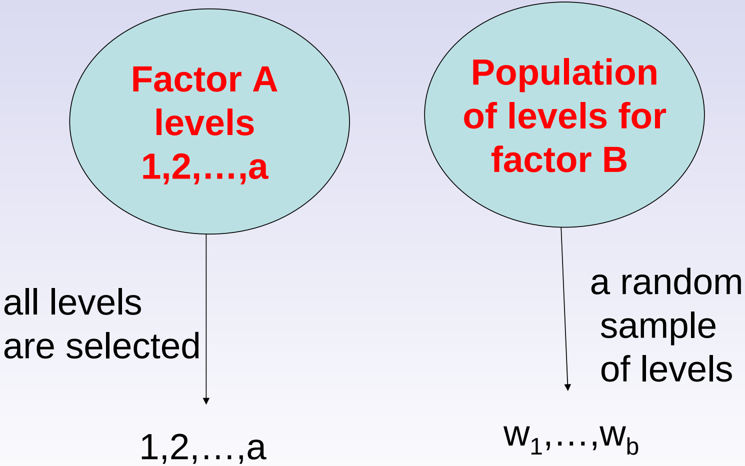
Conditional expected responses for selected levels

Denote $w_1, \cdots, w_b$ as b selected levels for factor B, and

$$M_{ij} = M(i, w_j), \quad i = 1, \cdots, a, \ j = 1, \cdots, b,$$

as the conditional expected responses. Note that for a different sample of levels, the conditional expected responses would be different, which reflects variation between levels.

Population and samples of levels



Two-way mixed effects model

The two-way mixed effects model assumes that

$$y_{ijk} = M_{ij} + \epsilon_{ijk}.$$

- i: level index of factor A, $i = 1, \cdots, a$
  j: level index of factor B, $j = 1, \cdots, b$
  k: observation index, $k = 1, \cdots, n_{ij}$
- y_{ijk}: kth observation at level i of factor A and level w_j of factor B
- M_{ij}: conditional expected response at level i of factor A and level w_j of factor B. $M_{ij} \sim N(\mu_i, \sigma^2_{all})$
- ϵ_{ijk}: random errors, $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$
- M_{ij} and ϵ_{ijk} are mutually independent

Two-way mixed effects model

The two-way random effects model can be written in the effect form as

$$y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \epsilon_{ijk}$$

- μ: overall mean
- α_i: effect at level i with $\sum_{i=1}^{a} \alpha_i = 0$.
  $\beta_j \overset{iid}{\sim} N(0, \sigma_b^2)$.
  $(\alpha\beta)_{ij} \overset{iid}{\sim} N(0, \sigma_{ab}^2)$
- ϵ_{ijk}: random errors, $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$
- β_j, $(\alpha\beta)_{ij}$ and ϵ_{ijk} are mutually independent

ANOVA table

For balanced designs with $n = n_{ij}$, we have

Source	df	SS	MS	E(MS)	F
A	$a-1$	SSA	MSA	$\sigma^2 + n\sigma^2_{ab} + Q(A)$	MSA/MSAB
B	$b-1$	SSB	MSB	$\sigma^2 + n\sigma^2_{ab} + na\sigma^2_b$	MSB/MSAB
AB	$(a-1)(b-1)$	SSAB	MSAB	$\sigma^2 + n\sigma^2_{ab}$	MSAB/MSE
error	$ab(n-1)$	SSE	MSE	σ^2	
Total	$abn-1$	SST			

$$Q(A) = nb\sum_{i=1}^{a}\alpha_i^2/(a-1)$$

SSA, SSB, SSAB, MSA, MSB, MSAB, SSE and MSE are the same as those in two-way fixed effects models.

F-tests

Note that $Q(A) = 0$ iff $\alpha_1 = \cdots = \alpha_a = 0$. We construct F statistics as follows.

$$
\begin{aligned}
\mathrm{H}_0 &: \sigma^2_{ab} = 0, \quad F = MSAB/MSE \\
\mathrm{H}_0 &: \sigma^2_{b} = 0, \quad F = MSB/MSAB \\
\mathrm{H}_0 &: \alpha_1 = \cdots = \alpha_a = 0, \quad F = MSA/MSAB
\end{aligned}
$$

For unbalanced designs, see previous comments for two-way random effects models.

SAS analysis of the machine data

Input data

```
options nocenter ps=64 ls=76;
data a;
   do machine=1 to 3;
      do person=1 to 6;
         do rep=1 to 3;
            input y @;
            output;
         end;
      end;
   end;
   cards;
   52.0 52.8 53.1
   51.8 52.8 53.1
   60.0 60.2 58.4
   51.1 52.3 50.3
   50.9 51.8 51.4
   46.4 44.8 49.2
   62.1 62.6 64.0
   59.7 60.0 59.0
   68.6 65.8 69.7
   63.2 62.8 62.2
   64.8 65.0 65.4
   43.7 44.2 43.0
   67.5 67.2 66.9
   61.5 61.7 62.3
   70.8 70.6 71.0
   64.1 66.2 64.0
   72.1 72.0 71.1
   62.0 61.4 60.5
   ;
```

SAS analysis of the machine data

Analysis of the balanced design

```
proc glm;
   class machine person;
   model y = machine | person;
   contrast 'machine 1 vs 2' machine 1 -1 0 /
             e=machine*person;
   random person machine*person / test;
   means machine;

proc varcomp method=type1;
   class machine person;
   model y = machine | person / fixed=1;

proc varcomp method=ml;
   class machine person;
   model y = machine | person / fixed=1;
```

SAS analysis of the machine data

SAS output for the balanced design

```
General Linear Models Procedure
Class Level Information
Class     Levels    Values
MACHINE        3    1 2 3
PERSON         6    1 2 3 4 5 6
Number of observateions in data set = 54


General Linear Models Procedure
Dependent Variable: Y
                          Sum of        Mean
Source            DF     Squares       Square     F Value   Pr > F
Model             17   3423.68833   201.39343    217.81    0.0001
Error             36     33.28667     0.92463
Corrected Total   53   3456.97500

                   R-Square   C.V.     Root MSE     Y Mean
                   0.990371 1.612031   0.96158     59.6500
```

SAS analysis of the machine data

```
Source            DF     Type I SS  Mean Square  F Value    Pr > F
MACHINE            2    1755.26333    877.63167   949.17    0.0001
PERSON             5    1241.89500    248.37900   268.63    0.0001
MACHINE*PERSON    10     426.53000     42.65300    46.13    0.0001

Source            DF   Type III SS  Mean Square  F Value    Pr > F
MACHINE            2    1755.26333    877.63167   949.17    0.0001
PERSON             5    1241.89500    248.37900   268.63    0.0001
MACHINE*PERSON    10     426.53000     42.65300    46.13    0.0001

                 Tests of Hypotheses Using the Type III
                 MS for machine*person as an Error Term
Contrast           DF    Contrast SS    Mean Square    F Value   Pr > F
machine 1 vs 2      1    571.2100000    571.2100000      13.39   0.0044
```

SAS analysis of the machine data

```
Source            Type III Expected Mean Square
MACHINE           Var(Error) + 3 Var(MACHINE*PERSON) + Q(MACHINE)
PERSON            Var(Error) + 3 Var(MACHINE*PERSON) + 9 Var(PERSON)
MACHINE*PERSON    Var(Error) + 3 Var(MACHINE*PERSON)

Tests of Hypotheses for Mixed Model Analysis of Variance
Dependent Variable: Y
Source: MACHINE
Error: MS(MACHINE*PERSON)
                             Denominator Denominator
     DF     Type III MS          DF            MS   F Value   Pr > F
      2    877.63166667          10        42.653   20.5761   0.0003
Source: PERSON
Error: MS(MACHINE*PERSON)
                             Denominator Denominator
     DF     Type III MS           DF           MS   F Value   Pr > F
      5         248.379           10       42.653    5.8232   0.0089
Source: MACHINE*PERSON
Error: MS(Error)
                             Denominator Denominator
     DF     Type III MS           DF           MS   F Value   Pr > F
     10          42.653           36 0.9246296296  46.1298   0.0001
```

SAS analysis of the machine data

```
Contrast            Contrast Expected Mean Square
machine 1 vs 2      Var(Error) + 3 Var(MACHINE*PERSON) + Q(MACHINE)

Level of          --------------Y--------------
MACHINE      N       Mean                 SD
1           18     52.3555556       3.98603772
2           18     60.3222222       8.16207554
3           18     66.2722222       4.19436675
```

SAS analysis of the machine data

Variance Components Estimation Procedure - Type I SS

```
Dependent Variable: Y
Source              DF        Type I SS         Type I MS
MACHINE              2     1755.26333333      877.63166667
PERSON               5     1241.89500000      248.37900000
MACHINE*PERSON      10      426.53000000       42.65300000
Error               36       33.28666667        0.92462963
Corrected Total     53     3456.97500000

Source         Expected Mean Square
MACHINE        Var(Error) + 3 Var(MACHINE*PERSON) + Q(MACHINE)
PERSON         Var(Error) + 3 Var(MACHINE*PERSON) + 9 Var(PERSON)
MACHINE*PERSON Var(Error) + 3 Var(MACHINE*PERSON)
Error          Var(Error)

Variance Component                Estimate
Var(PERSON)                    22.85844444
Var(MACHINE*PERSON)            13.90945679
Var(Error)                      0.92462963
```

SAS analysis of the machine data

Variance Components Estimation Procedure - MLE

```
Dependent Variable: Y
Iteration   Objective   Var(PERSON)   Var(MACHINE*PERSON)   Var(Error)
    0       72.219319    21.58853         13.13670919       0.87326132
    1       72.024604    19.16738         11.61461660       0.92177583
    2       72.024085    19.04906         11.54007435       0.92462082
    3       72.024085    19.04870         11.53984567       0.92462963
Convergence criteria met.

Asymptotic Covariance Matrix of Estimates
                      Var(PERSON)   Var(MACHINE*PERSON)   Var(Error)

Var(PERSON)            178.903082       -7.7986900         0.0000000
Var(MACHINE*PERSON)     -7.7986900      23.4013474        -0.0158322
Var(Error)               0.0000000      -0.0158322         0.0474967
```

SAS analysis of the machine data - unbalanced design

```
data b;
   set a;
   if (_N_=2 or _N_=3 or _N_=6 or _N_=8 or _N_=9 or _N_=12
       or _N_=19 or _N_=20 or _N_=27 or _N_=33) then delete;

proc glm;
   class machine person;
   model y = machine | person;
   random person machine*person / test;

proc varcomp method=type1;
   class machine person;
   model y = machine | person / fixed=1;
```

SAS analysis of the machine data - unbalanced design

```
The GLM Procedure
      Class Level Information
Class          Levels    Values
machine             3    1 2 3
person              6    1 2 3 4 5 6
Number of Observations Read          44
Number of Observations Used          44

The GLM Procedure
Dependent Variable: y
                             Sum of
Source            DF        Squares   Mean Square  F Value  Pr > F
Model             17    3061.743333    180.102549   206.41  <.0001
Error             26      22.686667      0.872564
Corrected Total   43    3084.430000

R-Square     Coeff Var      Root MSE        y Mean
0.992645      1.560754      0.934111      59.85000
```

SAS analysis of the machine data - unbalanced design

Source	DF	Type I SS	Mean Square	F Value	Pr > F
machine	2	1648.664722	824.332361	944.72	<.0001
person	5	1008.763583	201.752717	231.22	<.0001
machine*person	10	404.315028	40.431503	46.34	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
machine	2	1238.197626	619.098813	709.52	<.0001
person	5	1011.053834	202.210767	231.74	<.0001
machine*person	10	404.315028	40.431503	46.34	<.0001

SAS analysis of the machine data - unbalanced design

```
The GLM Procedure
Source          Type III Expected Mean Square
machine         Var(Error) + 2.137 Var(machine*person) + Q(machine)
person          Var(Error) + 2.2408 Var(machine*person) + 6.7224
                Var(person)
machine*person  Var(Error) + 2.3162 Var(machine*person)

The GLM Procedure
Tests of Hypotheses for Mixed Model Analysis of Variance
Dependent Variable: y
Source         DF    Type III SS    Mean Square   F Value   Pr > F
machine         2    1238.197626     619.098813     16.57   0.0007
Error     10.036      375.057436      37.370384
Error: 0.9226*MS(machine*person) + 0.0774*MS(Error)

Source        DF    Type III SS    Mean Square   F Value   Pr > F
person         5    1011.053834     202.210767      5.17   0.0133
Error     10.015     392.005726      39.143708
Error: 0.9674*MS(machine*person) + 0.0326*MS(Error)

Source              DF    Type III SS    Mean Square   F Value   Pr > F
machine*person      10     404.315028      40.431503     46.34   <.0001
Error: MS(Error)    26      22.686667       0.872564
```

SAS analysis of the machine data - unbalanced design

```
Variance Components Estimation Procedure
Class Level Information
Class     Levels    Values
MACHINE        3    1 2 3
PERSON         6    1 2 3 4 5 6
Number of observations in data set = 44
Variance Components Estimation Procedure
Dependent Variable: Y
Source                   DF       Type I SS         Type I MS
MACHINE                   2   1648.66472222      824.33236111
PERSON                    5   1008.76358308      201.75271662
MACHINE*PERSON           10    404.31502803       40.43150280
Error                    26     22.68666667        0.87256410
Corrected Total          43   3084.43000000
```

SAS analysis of the machine data - unbalanced design

```
Source              Expected Mean Square
MACHINE             Var(Error) + 2.6115 Var(MACHINE*PERSON)
                    + 0.1569 Var(PERSON) + Q(MACHINE)
PERSON              Var(Error) + 2.5866 Var(MACHINE*PERSON)
                    + 7.219 Var(PERSON)
MACHINE*PERSON      Var(Error) + 2.3162 Var(MACHINE*PERSON)
Error               Var(Error)

Variance Component               Estimate
Var(PERSON)                   21.70689884
Var(MACHINE*PERSON)           17.07910794
Var(Error)                     0.87256410
```

More complicated designs

Some experimental designs have *several sizes of experimental units* (SSEU). Examples of such designs are split-plot design (often used in agriculture), repeated measures (often used in biological and medical sciences) and nested designs.

SSEU designs

SSEU designs have the following characteristics:

- Treatment structure: at least two factors.
  Design structure: block designs (complete or incomplete)
- More than one size of EU. Each size of EU has its own design structure and treatment structure, and the model can be constructed from the structure of each size of EU. There is one error term for each size of EU. Thus we have more than one error term.

SSEU designs

SSEU designs have the following characteristics:

- Treatment structure: at least two factors.
  Design structure: block designs (complete or incomplete)
- More than one size of EU. Each size of EU has its own design structure and treatment structure, and the model can be constructed from the structure of each size of EU. There is one error term for each size of EU. Thus we have more than one error term.

Wheat data

An experiment was conducted to investigate how Fertility (factor A) and Variety (factor B) affect wheat yield. A field was divided into two blocks, each with four whole plots. Each of the four fertility levels was randomly assigned to one whole plot within each block. Each whole plot was split into two sub-plots, and each variety of wheat was randomly assigned to one sub-plot within each whole plot. Measurements at two levels of factor B in each whole plot are listed in each cell of the following table.

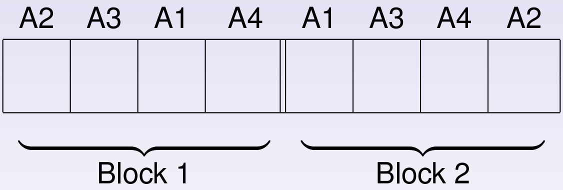
	A			
Block	1	2	3	4
1	35.4 37.9	36.7 38.2	34.8 36.4	39.5 40.0
2	41.6 40.3	42.7 41.6	43.6 42.8	44.5 47.6

Treatment structure and design structures

Treatment structure: two-way with Fertility (factor A) and Variety (factor B).
Design structures: we separate design structures for factor A and factor B.

Design structure for factor A

A field was divided into two blocks, and each block was divided into four whole plots to which four levels of the factor A were randomly assigned. The following figure shows one possible assignment.



EU for factor A: `whole plot`
Design structure for factor A: randomized complete block (RCB) design.

Design structure for factor B

First, ignoring the factor A and Block in the previous figure, we have 8 whole plots. Regard these whole plots as blocks. Each whole plot is further divided into two parts called `sub-plots`. Two levels of factor B were randomly assigned to these two sub-plots. The following figure shows one possible assignment.

B2	B2	B1	B2	B1	B1	B2	B2
B1	B1	B2	B1	B2	B2	B1	B1

EU for factor B: `sub-plot`
Design structure for factor B: randomized complete block (RCB) design.

Treatment structure and design structures

Putting Block and factor A back, we have the whole design

A2	A3	A1	A4	A1	A3	A4	A2
B2	B2	B1	B2	B1	B1	B2	B2
B1	B1	B2	B1	B2	B2	B1	B1

Block 1 Block 2

ANOVA tables

Since we have two different EU's, we can write two ANOVA tables and then put them together.

ANOVA table at the whole plot level:

Source	df
Block	1
A	3
Error(whole plot)	3

ANOVA table at the sub-plot level:

Source	df
whole plot (as block)	7
B	1
Sub-plot residual	7

ANOVA tables

Sub-plot residual contains variations due to the interaction between A and B, and sub-plot error:

SS(sub-plot residual)=SS(A*B)+SS(Error(sub-plot))

Therefore, the ANOVA table at the sub-plot level can be rewritten as

Source	df
whole plot (as block)	7
B	1
AB	3
Error (sub-plot)	4

ANOVA tables

Putting two tables together, we have

Source	df
Whole plot analysis	
Block	1
A	3
Error(whole plot)	3
Sub-plot analysis	
whole plot (as block)	7
B	1
AB	3
Error (sub-plot)	4

Split-plot model

In general, suppose that factor A has a levels, factor B has b levels and there are r blocks. We assume the following model

$$\begin{aligned} y_{ijk} = \mu \quad &+ \quad \rho_i + \alpha_j + e_{ij} && \text{(whole plot part of model)} \\ &+ \quad \beta_k + (\alpha\beta)_{jk} + \epsilon_{ijk} && \text{(sub-plot part of model)} \end{aligned}$$

- y_{ijk}: observation from the ith block, at level j of factor A and level k of factor B
- ρ_i: effect of the ith block. $\rho_i \overset{iid}{\sim} N(0, \sigma_b^2)$
- α_j, β_k and $(\alpha\beta)_{jk}$ are the same as those in the two-way fixed effects models with sum-to-zero side conditions.
- e_{ij}: whole plot errors, $e_{ij} \overset{iid}{\sim} N(0, \sigma_e^2)$
- ϵ_{ijk}: sub-plot errors, $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$
- ρ_i, e_{ij} and ϵ_{ijk} are mutually independent

Properties of the model

- Block effect is treated as random. It could also be treated as fixed, depending on the design and goal.
- The model is a mixed effects model.
- $E(y_{ijk}) = \mu + \alpha_j + \beta_k + (\alpha\beta)_{jk}$
  $\mathrm{Var}(y_{ijk}) = \sigma_b^2 + \sigma_e^2 + \sigma^2$

$$\mathrm{Cov}(y_{ijk}, y_{i'j'k'}) = \begin{cases} \sigma_b^2 + \sigma_e^2 & i = i',\ j = j', k \neq k' \\ \sigma_b^2 & i = i',\ j \neq j' \\ 0 & i \neq i' \end{cases}$$

ANOVA table

Source	df	SS	E(MS)
Block	$r-1$	SSBlock	$\sigma^2 + b\sigma_e^2 + ab\sigma_b^2$
A	$a-1$	SSA	$\sigma^2 + b\sigma_e^2 + \frac{rb}{a-1}\sum_{j=1}^{a}\alpha_j^2$
Error (whole plot)	$(a-1)(r-1)$	SSE(whole plot)	$\sigma^2 + b\sigma_e^2$
B	$b-1$	SSB	$\sigma^2 + \frac{ra}{b-1}\sum_{k=1}^{b}\beta_k^2$
AB	$(a-1)(b-1)$	SSAB	$\sigma^2 + \frac{r}{(a-1)(b-1)}\sum_{j=1}^{a}\sum_{k=1}^{b}(\alpha\beta)_{jk}^2$
Error (sub-plot)	$a(b-1)(r-1)$	SSE(sub-plot)	σ^2
Total	$abr-1$	SST	

ANOVA table

$$
\begin{aligned}
\text{SSBlock} &= ab\sum_{i=1}^{r}(\bar{y}_{i..}-\bar{y}_{...})^2 \\
\text{SSA} &= br\sum_{j=1}^{a}(\bar{y}_{.j.}-\bar{y}_{...})^2 \\
SSE(wholeplot) &= b\sum_{i=1}^{r}\sum_{j=1}^{a}(\bar{y}_{ij.}-\bar{y}_{i..}-\bar{y}_{.j.}+\bar{y}_{...})^2 \\
SSB &= ar\sum_{k=1}^{b}(\bar{y}_{..k}-\bar{y}_{...})^2 \\
SSAB &= r\sum_{j=1}^{a}\sum_{k=1}^{b}(\bar{y}_{.jk}-\bar{y}_{.j.}-\bar{y}_{..k}+\bar{y}_{...})^2 \\
SSE(sub-plot) &= \sum_{i=1}^{r}\sum_{j=1}^{a}\sum_{k=1}^{b}(y_{ijk}-\bar{y}_{.jk}-\bar{y}_{ij.}+\bar{y}_{.j.})^2 \\
SST &= \sum_{i=1}^{r}\sum_{j=1}^{a}\sum_{k=1}^{b}(y_{ijk}-\bar{y}_{...})^2
\end{aligned}
$$

F tests

Test	H_0	Under H_0	F
A	$\alpha_1 = \cdots = \alpha_a = 0$	$\sum_{j=1}^{a} \alpha_j^2 = 0$	MSA/MSE(whole plot)
B	$\beta_1 = \cdots = \beta_b = 0$	$\sum_{k=1}^{b} \beta_j^2 = 0$	MSB/MSE(sub-plot)
AB	$(\alpha\beta)_{jk} = 0$ all j, k	$\sum_{j=1}^{a} \sum_{k=1}^{b} (\alpha\beta)_{jk}^2 = 0$	MSAB/MSE(sub-plot)

Estimation of parameters

$$
\begin{aligned}
\hat{\sigma}^2 &= MSE(\text{sub-plot}) \\
\hat{\sigma}_e^2 &= (MSE(\text{whole plot}) - MSE(\text{sub-plot}))/b \\
\hat{\mu} &= \bar{y}_{...} \\
\hat{\alpha}_j &= \bar{y}_{.j.} - \bar{y}_{...} \\
\hat{\beta}_k &= \bar{y}_{..k} - \bar{y}_{...} \\
\hat{\alpha\beta}_{jk} &= \bar{y}_{.jk} - \bar{y}_{.j.} - \bar{y}_{..k} + \bar{y}_{...}
\end{aligned}
$$

SAS analysis of the wheat data

Input data and plot

```
data a;
   do block=1 to 2;
     do A=1 to 4;
       do B=1 to 2;
         input yield @;
         s = (block-1)*2+B;
         output;
       end;
     end;
   end;
   cards;
   35.4 37.9 36.7 38.2 34.8 36.4 39.5 40.0
   41.6 40.3 42.7 41.6 43.6 42.8 44.5 47.6
   ;
```

SAS analysis of the wheat data

Plot data and fit a split-plot model

```
proc plot vpercent=50;
   plot yield*A=s;

proc glm;
   class block A B;
   model yield = block A block*A B A*B;
   random block block*A / test;
   /* use block*A as error mean square */
   means A / tukey e=block*A;
   means B A*B / tukey;
```

SAS analysis of the wheat data

```
       50 +
         |
         |
         |                                                              4
         |
         |
         |
       45 +
         |                                                              3
         |                                          3
   YIELD |                      3                   4
         |
         |  3                   4
         |
       40 +  4                                                           2
         |                                                              1
         |
         |  2                   2
         |
         |                      1                   2
         |  1
       35 +                                          1
         ---+-------------------+-------------------+-------------------+--
            1                   2                   3                   4
                                          A
```

SAS output of the wheat data

```
General Linear Models Procedure
Class Level Information
Class     Levels    Values
BLOCK          2    1 2
A              4    1 2 3 4
B              2    1 2
Number of observations in data set = 16


General Linear Models Procedure
Dependent Variable: YIELD
                          Sum of         Mean
Source            DF     Squares       Square   F Value   Pr > F
Model             11  182.020000    16.547273      7.85   0.0306
Error              4    8.430000     2.107500
Corrected Total   15  190.450000

        R-Square       C.V.    Root MSE     YIELD Mean
        0.955736   3.609007     1.45172        40.2250
```

SAS output of the wheat data

Source	DF	Type I SS	Mean Square	F Value	Pr > F
BLOCK	1	131.102500	131.102500	62.21	0.0014
A	3	40.190000	13.396667	6.36	0.0530
BLOCK*A	3	6.927500	2.309167	1.10	0.4476
B	1	2.250000	2.250000	1.07	0.3599
A*B	3	1.550000	0.516667	0.25	0.8612

Source	DF	Type III SS	Mean Square	F Value	Pr > F
BLOCK	1	131.102500	131.102500	62.21	0.0014
A	3	40.190000	13.396667	6.36	0.0530
BLOCK*A	3	6.927500	2.309167	1.10	0.4476
B	1	2.250000	2.250000	1.07	0.3599
A*B	3	1.550000	0.516667	0.25	0.8612

SAS output of the wheat data

```
General Linear Models Procedure
Source        Type III Expected Mean Square
BLOCK         Var(Error) + 2 Var(BLOCK*A) + 8 Var(BLOCK)
A             Var(Error) + 2 Var(BLOCK*A) + Q(A,A*B)
BLOCK*A       Var(Error) + 2 Var(BLOCK*A)
B             Var(Error) + Q(B,A*B)
A*B           Var(Error) + Q(A*B)
General Linear Models Procedure
Tests of Hypotheses for Mixed Model Analysis of Variance
Dependent Variable: YIELD
Source: BLOCK
Error: MS(BLOCK*A)
                 Denominator   Denominator
DF  Type III MS           DF            MS  F Value  Pr > F
1      131.1025            3  2.3091666667  56.7748  0.0048
Source: A *
Error: MS(BLOCK*A)
                 Denominator  Denominator
DF  Type III MS           DF           MS   F Value  Pr > F
3  13.39666666         7   3  2.309166667    5.8015  0.0914
* - This test assumes one or more other fixed effects are zero
```

SAS output of the wheat data

```
Source: BLOCK*A
Error: MS(Error)
                        Denominator   Denominator
DF   Type III MS                 DF            MS     F Value   Pr > F
3    2.309166667                  4        2.1075      1.0957   0.4476
Source: B *
Error: MS(Error)
                        Denominator   Denominator
DF   Type III MS                 DF            MS     F Value   Pr > F
1           2.25                  4        2.1075      1.0676   0.3599
* - This test assumes one or more other fixed effects are zero
Source: A*B
Error: MS(Error)
                        Denominator   Denominator
DF   Type III MS                 DF            MS     F Value   Pr > F
3    0.516666667                  4        2.1075      0.2452   0.8612
```

SAS output of the wheat data

```
Tukey's Studentized Range (HSD) Test for variable: YIELD
NOTE: This test controls the type I experimentwise error
      rate, but generally has a higher type II error rate
      than REGWQ.
Alpha= 0.05  df= 3  MSE= 2.309167
Critical Value of Studentized Range= 6.825
Minimum Significant Difference= 5.1853
Means with the same letter are not significantly different.

          Tukey Grouping           Mean      N  A
                 A               42.900      4  4
                 A
                 A               39.800      4  2
                 A
                 A               39.400      4  3
                 A
                 A               38.800      4  1
```

SAS output of the wheat data

```
Tukey's Studentized Range (HSD) Test for variable: YIELD
NOTE: This test controls the type I experimentwise error
      rate, but generally has a higher type II error rate
      than REGWQ.
Alpha= 0.05  df= 4  MSE= 2.1075
Critical Value of Studentized Range= 3.927
Minimum Significant Difference= 2.0153
Means with the same letter are not significantly different.

        Tukey Grouping            Mean       N   B
                 A             40.6000       8   2
                 A
                 A             39.8500       8   1

Level of   Level of         ------------YIELD------------
A          B          N       Mean                SD
1          1          2     38.5000000        4.38406204
1          2          2     39.1000000        1.69705627
2          1          2     39.7000000        4.24264069
2          2          2     39.9000000        2.40416306
3          1          2     39.2000000        6.22253967
3          2          2     39.6000000        4.52548340
4          1          2     42.0000000        3.53553391
4          2          2     43.8000000        5.37401154
```

Repeated measures

Repeated measures data arise in many areas of investigation such as agriculture, pharmacokinetics, epidemiology, medicine and social science. They are generated by observing each of a number of subjects repeatedly over time or under varying conditions.

Drug example An experiment was conducted to investigate the effects of three drugs: AX23 (coded as 1), BWW9 (coded as 2) and Control (coded as 3). Each drug was administered to eight different subjects. Each person's heart rate was then measured every 5 minutes for 4 time intervals. Observations are listed in the following table.

Drug data

subject within drug	AX23				BWW9				control			
	T_1	T_2	T_3	T_4	T_1	T_2	T_3	T_4	T_1	T_2	T_3	T_4
1	72	86	81	77	85	86	83	80	69	73	72	74
2	78	83	88	81	82	86	80	84	66	62	67	73
3	71	82	81	75	71	78	70	75	84	90	88	87
4	72	83	83	69	83	88	79	81	80	81	77	72
5	66	79	77	66	86	85	76	76	72	72	69	70
6	74	83	84	77	85	82	83	80	65	62	65	61
7	62	73	78	70	79	83	80	81	75	69	69	68
8	69	75	76	70	83	84	78	81	71	70	65	65

Repeated measures

In general, structures of repeated measures are the same as the split-plot designs: at least two factors, block designs, and two sizes of EUs. The difference is that time is often a factor that cannot be randomly assigned to its EUs.

For the drug example, we have a two-way treatment structure.

Factor A: `drug` (3 levels)

EU for A: subject (whole plot)

Design structure for A: completely randomized design

Factor B: `time` (4 levels)

EU for B: time intervals (sub-plot) between time measurements, or the interval of time during which the subject is exposed to a drug.

Design structure for B: we cannot randomly assign time to time intervals.

Repeated measures

Consequence: measurements overtime (sub-plot) on the same subject (whole plot) are likely to be correlated (if the heart rate is high now, it is likely to remain high for a while). The usual split plot analysis may not be valid.
Question: under what situation the usual split plot analysis is still valid?

Model

In general, suppose that n_i subjects were randomly assigned to drug i, and each subject was measured t times. We assume the following model

$$\begin{aligned} y_{ijk} = \mu \quad &+ \quad \alpha_i + e_{ik} && \text{(whole plot part of model)} \\ &+ \quad \beta_j + (\alpha\beta)_{ij} + \epsilon_{ijk} && \text{(sub-plot part of model)} \end{aligned}$$

- y_{ijk}: observation at time j from subject k who was assigned to drug i
- α_i and β_j are main effects of drug and time respectively. $(\alpha\beta)_{ij}$ is the interaction between drug and time. Usual side conditions are assumed
- e_{ik}: whole plot errors
- ϵ_{ijk}: sub-plot errors

Correlation

We made the following assumptions for the split-plot design:

- $e_{ik} \overset{iid}{\sim} N(0, \sigma_e^2)$
- $\epsilon_{ijk} \overset{iid}{\sim} N(0, \sigma^2)$
- e_{ij} and ϵ_{ijk} are mutually independent

These independence assumptions may no longer be appropriate for repeated measures. Fortunately, the split-plot analysis is valid under more general assumptions. That is, under more general assumptions specified later, the F ratios computed in the ANOVA table for split-plot designs will still have F distributions under corresponding null hypotheses.

Notations

Let

$$\boldsymbol{\epsilon}_{ik} = \begin{pmatrix} \epsilon_{i1k} \\ \vdots \\ \epsilon_{itk} \end{pmatrix}, \quad \boldsymbol{e}_i = \begin{pmatrix} e_{i1} \\ \vdots \\ e_{in_i} \end{pmatrix}.$$

- $\boldsymbol{\epsilon}_{ik}$ is vector of time interval errors for subject k receiving drug i.
- $\boldsymbol{e}_i$ is the vector of subject errors for drug i.

Denote the covariance matrices of $\boldsymbol{\epsilon}_{ik}$ and $\boldsymbol{e}_i$ by

$$\mathrm{Cov}(\boldsymbol{\epsilon}_{ik}) = \boldsymbol{\Sigma}, \quad \mathrm{Cov}(\boldsymbol{e}_i) = \boldsymbol{\Lambda}.$$

Compound symmetry

A covariance matrix is of `compound symmetry` form if it can be expressed as

$$\sigma^2 \begin{bmatrix} 1 & \rho & \cdots & \rho \\ \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \vdots & \vdots \\ \rho & \rho & \cdots & 1 \end{bmatrix}$$

Fact A `sufficient` condition for the F-tests of the usual split-plot analysis of variance to be valid is that both $\boldsymbol{\Sigma}$ and $\boldsymbol{\Lambda}$ have the form of compound symmetry.

Sphericity condition

A covariance matrix satisfies the `sphericity condition` (Huynh-Feldt condition, type H) if it can be expressed as

$$\sigma^2 \begin{bmatrix} 1+2\lambda_1 & \lambda_1+\lambda_2 & \cdots & \lambda_1+\lambda_p \\ \lambda_1+\lambda_2 & 1+2\lambda_2 & \cdots & \lambda_2+\lambda_p \\ \vdots & \vdots & \vdots & \vdots \\ \lambda_1+\lambda_p & \lambda_2+\lambda_p & \cdots & 1+2\lambda_p \end{bmatrix}$$

Fact The `necessary and sufficient` condition for the F-tests of the usual split-plot analysis of variance to be valid is that both $\boldsymbol{\Sigma}$ and $\boldsymbol{\Lambda}$ satisfy the spherity condition.
The spherity condition can be checked by the Mauchly's test for spherity.

Adjustment for correlation

If the sphericity conditions are met, then there are $t-1$ degrees of freedom per subject over time. If not, there should be somewhat less due to correlation. The worst-case scenario, or the most conservative approach, would suppose that there is only one piece of information (degree of freedom) over time. On the other hand, minor violations of the sphericity conditions might encourage minor adjustments to the degrees of freedom.

Adjustment for correlation

There are two approaches: `Greenhouse-Geisser` (G-G) and `Huynh-Feldt` (H-F) adjustments. Both of them estimate a quantity called ϵ which measures the deviation from sphericity conditions. In theory, $\epsilon \leq 1$ and $\epsilon = 1$ iff the sphericity conditions hold. To adjust the degrees of freedom, rather than compare the F ratios to the usual critical values with a and b numerator and denominator degrees of freedom, compare them to F critical values with ϵa and ϵb numerator and denominator degrees of freedom.

Limitations

- The method is applicable in the case where the data are balanced: measurements were taken at the same times for all subjects, no missing values.
- It does not explore change over time (trajectory) directly, which is often of interest.
- The sphericity conditions are often violated and the adjustments are often too conservative.

More advanced methods include multivariate analysis and mixed effects models.

Limitations

- The method is applicable in the case where the data are balanced: measurements were taken at the same times for all subjects, no missing values.
- It does not explore change over time (trajectory) directly, which is often of interest.
- The sphericity conditions are often violated and the adjustments are often too conservative.

More advanced methods include multivariate analysis and mixed effects models.

Limitations

- The method is applicable in the case where the data are balanced: measurements were taken at the same times for all subjects, no missing values.
- It does not explore change over time (trajectory) directly, which is often of interest.
- The sphericity conditions are often violated and the adjustments are often too conservative.

More advanced methods include multivariate analysis and mixed effects models.

Limitations

- The method is applicable in the case where the data are balanced: measurements were taken at the same times for all subjects, no missing values.
- It does not explore change over time (trajectory) directly, which is often of interest.
- The sphericity conditions are often violated and the adjustments are often too conservative.

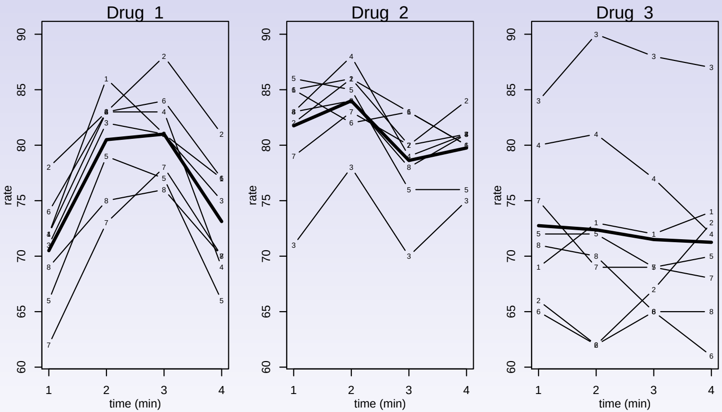
More advanced methods include multivariate analysis and mixed effects models.

Analysis of the drug data

```
> drug <- rep(1:3,rep(32,3))
> time <- rep(1:4, 24)
> rate <- c(72,86,81,77,78,83,88,81,71,82,81,75,72,83,83,69,
            66,79,77,66,74,83,84,77,62,73,78,70,69,75,76,70,
            85,86,83,80,82,86,80,84,71,78,70,75,83,88,79,81,
            86,85,76,76,85,82,83,80,79,83,80,81,83,84,78,81,
            69,73,72,74,66,62,67,73,84,90,88,87,80,81,77,72,
            72,72,69,70,65,62,65,61,75,69,69,68,71,70,65,65)

> pdf("drug.pdf", pointsize=9, width=4, height=2.8)
> par(mfrow=c(1,3), mgp=c(2,1,0), mar=c(3,3,1,1)+.1)
> x <- 1:4
> for (j in 1:3) {
    meanrate <- sapply(split(rate[drug==j],time[drug==j]),mean)
    plot(x,meanrate,xlab="time (min)", ylab="rate", xaxt="n",
         type="l", lwd=3, ylim=range(rate))
    axis(side=1, at=x)
    for (i in 1:8) lines(x, rate[drug==j][(1+(i-1)*4):(i*4)],
         type="b", pch=as.character(i),cex=.6)
    mtext(paste("Drug ",as.character(j)))
}
> dev.off()
```

Analysis of the drug data



Analysis of the drug data

Input data

```
options nocenter ps=64 ls=76;
data a;
   do drug=1 to 3;
     do person=1 to 8;
       do time=1 to 4;
         input rate @;
         output;
       end;
     end;
   end;
   cards;
   72 86 81 77 78 83 88 81 71 82 81 75 72 83 83 69
   66 79 77 66 74 83 84 77 62 73 78 70 69 75 76 70
   85 86 83 80 82 86 80 84 71 78 70 75 83 88 79 81
   86 85 76 76 85 82 83 80 79 83 80 81 83 84 78 81
   69 73 72 74 66 62 67 73 84 90 88 87 80 81 77 72
   72 72 69 70 65 62 65 61 75 69 69 68 71 70 65 65
   ;
```

Analysis of the drug data

Compute means and plot

```
proc sort;
   by drug time;

proc means noprint;
   by drug time;
   var rate;
   output out=b mean=mrate;

proc plot vpercent=50;
   plot mrate*time=drug;
```

Analysis of the drug data

```
         Plot of mrate*time.  Symbol is value of drug.
   85 +
      |                   2
      |
      |
      |
      |  2
      |                   1                1
   80 +                                                     2
      |
      |                                    2
mrate |
      |
      |
      |
   75 +
      |
      |
      |  3                                                  1
      |                   3
      |                                    3                3
      |  1
   70 +
      ---+----------------+----------------+----------------+--
         1                2                3                4
                                 time
```

Analysis of the drug data

Univariate analysis

```
proc glm data=a;
   class drug person time;
/* Persons are different for different drugs.
   Thus person is nested within drug */
   model rate = drug person(drug) time drug*time;
   test h=drug e=person(drug);
/* use person(drug) as error mean square */
   means drug / bon e=person(drug);
   means time time*drug / bon;
```

Analysis of the drug data

```
The GLM Procedure
        Class Level Information
Class          Levels    Values
drug                3    1 2 3
person              8    1 2 3 4 5 6 7 8
time                4    1 2 3 4
Number of Observations Read          96
Number of Observations Used          96

The GLM Procedure
Dependent Variable: rate
                              Sum of
Source                 DF    Squares   Mean Square  F Value  Pr > F
Model                  32  4449.020833  139.031901    19.10  <.0001
Error                  63   458.468750    7.277282
Corrected Total        95  4907.489583
R-Square     Coeff Var     Root MSE     rate Mean
0.906578      3.529696     2.697644      76.42708
```

Analysis of the drug data

Source	DF	Type I SS	Mean Square	F Value	Pr > F
drug	2	1315.083333	657.541667	90.36	<.0001
person(drug)	21	2320.156250	110.483631	15.18	<.0001
time	3	282.614583	94.204861	12.95	<.0001
drug*time	6	531.166667	88.527778	12.16	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
drug	2	1315.083333	657.541667	90.36	<.0001
person(drug)	21	2320.156250	110.483631	15.18	<.0001
time	3	282.614583	94.204861	12.95	<.0001
drug*time	6	531.166667	88.527778	12.16	<.0001

Tests of Hypotheses Using the Type III
MS for person(drug) as an Error Term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
drug	2	1315.083333	657.541667	5.95	0.0090

Analysis of the drug data

```
Bonferroni (Dunn) t Tests for rate
NOTE: This test controls the Type I experimentwise error rate,
but it generally has a higher Type II error rate than REGWQ.

Alpha                                   0.05
Error Degrees of Freedom                  21
Error Mean Square                   110.4836
Critical Value of t                  2.60135
Minimum Significant Difference        6.8358
Means with the same letter are not significantly different.

Bon Grouping   Mean      N    drug
     A        81.031     32     2
B    A        76.281     32     1
B             71.969     32     3
```

Analysis of the drug data

```
Bonferroni (Dunn) t Tests for rate
NOTE: This test controls the Type I experimentwise error rate,
but it generally has a higher Type II error rate than REGWQ.

Alpha                                   0.05
Error Degrees of Freedom                  63
Error Mean Square                   7.277282
Critical Value of t                  2.72412
Minimum Significant Difference        2.1214
Means with the same letter are not significantly different.
Bon Grouping   Mean      N    time
     A       78.9583     24    2
B    A       77.0417     24    3
B    C       75.0000     24    1
     C       74.7083     24    4
```

Analysis of the drug data

Level of drug	Level of time	N	rate Mean	rate Std Dev
1	1	8	70.5000000	4.89897949
1	2	8	80.5000000	4.47213595
1	3	8	81.0000000	4.00000000
1	4	8	73.1250000	5.11126208
2	1	8	81.7500000	4.86239212
2	2	8	84.0000000	3.07059789
2	3	8	78.6250000	4.20671232
2	4	8	79.7500000	2.91547595
3	1	8	72.7500000	6.62786326
3	2	8	72.3750000	9.39509751
3	3	8	71.5000000	7.74596669
3	4	8	71.2500000	7.70435869

Analysis of the drug data

Same analysis with repeated statement

```
/* To convert the univariate data form to the
multivariate form and conduct multivariate analysis */
proc sort data=a;
   by drug person;

data new(keep=r1-r4 drug);
   array r(4) r1-r4;
   do time=1 to 4;
      set a;
      by drug person;
      r(time)=rate;
      if last.person then return;
   end;

proc print data=new;
```

Analysis of the drug data

Obs	r1	r2	r3	r4	drug
1	72	86	81	77	1
2	78	83	88	81	1
3	71	82	81	75	1
4	72	83	83	69	1
5	66	79	77	66	1
6	74	83	84	77	1
7	62	73	78	70	1
8	69	75	76	70	1
9	85	86	83	80	2
10	82	86	80	84	2
11	71	78	70	75	2
12	83	88	79	81	2
13	86	85	76	76	2
14	85	82	83	80	2
15	79	83	80	81	2
16	83	84	78	81	2
17	69	73	72	74	3
18	66	62	67	73	3
19	84	90	88	87	3
20	80	81	77	72	3
21	72	72	69	70	3
22	65	62	65	61	3
23	75	69	69	68	3
24	71	70	65	65	3

Analysis of the drug data

```
proc glm data=new;
   class drug;
   model r1-r4=drug / nouni;
   repeated time 4 (0 1 2 3) polynomial / printe nom
                                          summary;
/* printe asks for the test of sphericity
   nom: no multivariate, just the univariate
   repeated measure analysis */
```

Analysis of the drug data

```
The GLM Procedure
   Class Level Information
Class           Levels    Values
drug                 3    1 2 3
Number of Observations Read          24
Number of Observations Used          24
The GLM Procedure
Repeated Measures Analysis of Variance
           Repeated Measures Level Information
Dependent Variable         r1        r2        r3        r4
     Level of time          0         1         2         3
Partial Correlation Coefficients from the Error SSCP Matrix/Prob>|r|
DF = 21             r1             r2             r3             r4
r1            1.000000       0.828050       0.825500       0.644458
                               <.0001         <.0001         0.0012
r2            0.828050       1.000000       0.837311       0.722279
                <.0001                        <.0001         0.0001
r3            0.825500       0.837311       1.000000       0.834635
                <.0001         <.0001                        <.0001
r4            0.644458       0.722279       0.834635       1.000000
                0.0012         0.0001         <.0001
```

Analysis of the drug data

```
                    E = Error SSCP Matrix
time_N represents the nth degree polynomial contrast for time
               time_1         time_2         time_3
time_1       245.1813        37.9712        -1.2312
time_2        37.9712       103.1563       -31.3189
time_3        -1.2312       -31.3189       110.1313
 Partial Correlation Coefficients from the Error SSCP Matrix of the
   Variables Defined by the Specified Transformation / Prob > |r|
DF = 21         time_1         time_2         time_3
time_1        1.000000       0.238761      -0.007493
                               0.2846         0.9736
time_2        0.238761       1.000000      -0.293835
                0.2846                        0.1844
time_3       -0.007493      -0.293835       1.000000
                0.9736         0.1844
```

Analysis of the drug data

Sphericity Tests

Variables	DF	Mauchly's Criterion	Chi-Square	Pr > ChiSq
Transformed Variates	5	0.6693259	7.9181595	0.1608
Orthogonal Components	5	0.6693259	7.9181595	0.1608

The GLM Procedure
Repeated Measures Analysis of Variance
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
drug	2	1315.083333	657.541667	5.95	0.0090
Error	21	2320.156250	110.483631		

Analysis of the drug data

```
The GLM Procedure
Repeated Measures Analysis of Variance
Univariate Tests of Hypotheses for Within Subject Effects
Source           DF   Type III SS   Mean Square  F Value  Pr > F
time              3   282.6145833    94.2048611    12.95  <.0001
time*drug         6   531.1666667    88.5277778    12.16  <.0001
Error(time)      63   458.4687500     7.2772817

                          Adj Pr > F
Source                   G - G     H - F
time                    <.0001    <.0001
time*drug               <.0001    <.0001
Error(time)

Greenhouse-Geisser Epsilon    0.7986
Huynh-Feldt Epsilon           0.9944
```

Analysis of the drug data

```
The GLM Procedure
Repeated Measures Analysis of Variance
Analysis of Variance of Contrast Variables
time_N represents the nth degree polynomial contrast for time

Contrast Variable: time_1
Source        DF    Type III SS    Mean Square   F Value   Pr > F
Mean           1      9.3520833      9.3520833      0.80   0.3809
drug           2     82.0166667     41.0083333      3.51   0.0483
Error         21    245.1812500     11.6752976

Contrast Variable: time_2
Source        DF    Type III SS    Mean Square   F Value   Pr > F
Mean           1    237.5104167    237.5104167     48.35   <.0001
drug           2    404.0833333    202.0416667     41.13   <.0001
Error         21    103.1562500      4.9122024

Contrast Variable: time_3
Source        DF    Type III SS    Mean Square   F Value   Pr > F
Mean           1     35.7520833     35.7520833      6.82   0.0163
drug           2     45.0666667     22.5333333      4.30   0.0273
Error         21    110.1312500      5.2443452
```

Nested designs

In a given experimental design, it is possible to have nested effects in the design structure, the treatment structure, or both. Factors may be all fixed, all random, or both. Thus we may have fixed, random or mixed models.
Nesting occurs most often in the design structure where a smaller experimental unit is nested within a larger one. Therefore, there are more than one size of EU. We have learned split-plot and repeated measures.

Nesting in treatment structure In a treatment structure, the levels of factor A are nested within the levels of factor B if each level of A occurs with only one level of factor B.

Lab example

In a cooperative trial in analytical chemistry, seven specimens were sent to six laboratories, each three times a month apart for duplicated analysis. The response is the concentration of (unspecified) analyte in g/kg. The purpose of the study was to assess components of variation in cooperative trials. We use the data from Specimen 1 shown in the following table.

	Laboratory					
Batch	1	2	3	4	5	6
1	0.29	0.40	0.40	0.90	0.44	0.38
	0.33	0.40	0.35	1.30	0.44	0.39
2	0.33	0.43	0.38	0.90	0.45	0.40
	0.32	0.36	0.32	1.10	0.45	0.46
3	0.34	0.42	0.38	0.90	0.42	0.72
	0.31	0.40	0.33	0.90	0.46	0.79

Lab example

Treatment structure: two-way `Lab` and `Bat`. Even though they are all labeled as 1, 2, and 3, three batches in different laboratories are different. Therefore, the factor `Bat` is nested with `Lab`. Levels of both factors are random samples from their corresponding populations. Therefore, they are random factors.
Design structure: completely randomized design

Model

In general, suppose that we have two random factors, A and B, and B is nested within A. We consider the following model

$$\begin{aligned} y_{ijk} &= \mu + \alpha_i + \beta_{j(i)} + \epsilon_{ijk}, \\ & \quad i = 1, \cdots, a;\ j = 1, \cdots, b;\ k = 1, \cdots, n \end{aligned}$$

- y_{ijk}: response for level i of factor A, level j of factor B and duplicate k
- μ: overall mean
- α_i: effects of factor A, $\alpha_i \stackrel{iid}{\sim} N(0, \sigma_a^2)$
- $\beta_{j(i)}$: effects of factor B, $\beta_{j(i)} \stackrel{iid}{\sim} N(0, \sigma_b^2)$
- ϵ_{ijk}: random errors, $\epsilon_{ijk} \stackrel{iid}{\sim} N(0, \sigma^2)$
- α_i, $\beta_{j(i)}$ and ϵ_{ijk} are mutually independent

ANOVA table

Source	df	SS	MS	E(MS)	F
A	$a-1$	SSA	MSA	$\sigma^2 + n\sigma_b^2 + bn\sigma_a^2$	MSA/MSB
B	$a(b-1)$	SSB	MSB	$\sigma^2 + n\sigma_b^2$	MSB/MSE
error	$ab(n-1)$	SSE	MSE	σ^2	
Total	$abn-1$	SST			

$$
\begin{aligned}
SSA &= bn\sum_{i=1}^{a}(\bar{y}_{i..} - \bar{y}_{...})^2, \\
SSB &= n\sum_{i=1}^{a}\sum_{j=1}^{b}(\bar{y}_{ij.} - \bar{y}_{i..})^2, \\
SSE &= \sum_{i=1}^{a}\sum_{j=1}^{b}(y_{ijk} - \bar{y}_{ij.})^2, \\
SST &= SSA + SSB + SSE.
\end{aligned}
$$

F tests

We construct F statistics as follows.

$$
\begin{aligned}
\mathrm{H}_0 &: \sigma_a^2 = 0, \quad F = MSA/MSB \\
\mathrm{H}_0 &: \sigma_b^2 = 0, \quad F = MSB/MSE
\end{aligned}
$$

Analysis of lab data

```
options nocenter ps=64 ls=76;
data a;
   do Lab=1 to 6;
      do Bat=1 to 3;
         do rep=1 to 2;
            input y @;
            output;
         end;
      end;
   end;
   cards;
   0.29 0.33 0.33 0.32 0.34 0.31
   0.40 0.40 0.43 0.36 0.42 0.40
   0.40 0.35 0.38 0.32 0.38 0.33
   0.90 1.30 0.90 1.10 0.90 0.90
   0.44 0.44 0.45 0.45 0.42 0.46
   0.38 0.39 0.40 0.46 0.72 0.79
   ;
```

Analysis of lab data

```
proc glm;
   class Lab Bat;
   model y = Lab Bat(Lab);
   random Lab Bat(Lab) / test;

proc varcomp method=type1;
   class Lab Bat;
   model y = Lab Bat(Lab)
```

Analysis of lab data

```
The GLM Procedure
      Class Level Information
Class          Levels    Values
Lab                 6    1 2 3 4 5 6
Bat                 3    1 2 3
Number of Observations Read          36
Number of Observations Used          36

The GLM Procedure
Dependent Variable: y
                              Sum of
Source              DF       Squares   Mean Square  F Value  Pr > F
Model               17    2.09461389    0.12321258    19.57  <.0001
Error               18    0.11335000    0.00629722
Corrected Total     35    2.20796389

R-Square     Coeff Var      Root MSE        y Mean
0.948663      15.61936      0.079355      0.508056

Source              DF     Type I SS   Mean Square  F Value  Pr > F
Lab                  5    1.89021389    0.37804278    60.03  <.0001
Bat(Lab)            12    0.20440000    0.01703333     2.70  0.0277
```

Analysis of lab data

```
The GLM Procedure
Source                  Type III Expected Mean Square
Lab                     Var(Error) + 2 Var(Bat(Lab)) + 6 Var(Lab)
Bat(Lab)                Var(Error) + 2 Var(Bat(Lab))

The GLM Procedure
Tests of Hypotheses for Random Model Analysis of Variance
Dependent Variable: y

Source                 DF   Type III SS   Mean Square  F Value  Pr > F
Lab                     5      1.890214      0.378043    22.19  <.0001
Error: MS(Bat(Lab))    12      0.204400      0.017033

Source                 DF   Type III SS   Mean Square  F Value  Pr > F
Bat(Lab)               12      0.204400      0.017033     2.70  0.0277
Error: MS(Error)       18      0.113350      0.006297
```

Analysis of lab data

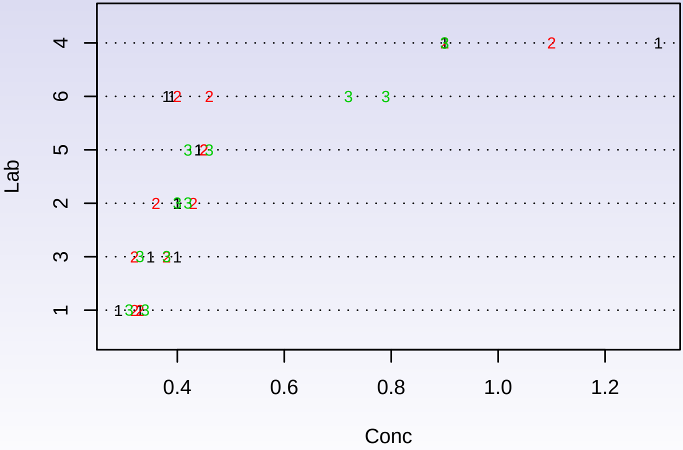
```
Dependent Variable:    y
               Type 1 Analysis of Variance
                                       Sum of
Source                 DF             Squares      Mean Square
Lab                     5            1.890214         0.378043
Bat(Lab)               12            0.204400         0.017033
Error                  18            0.113350         0.006297
Corrected Total        35            2.207964                .
                Type 1 Analysis of Variance
Source                   Expected Mean Square
Lab                      Var(Error) + 2 Var(Bat(Lab)) + 6 Var(Lab)
Bat(Lab)                 Var(Error) + 2 Var(Bat(Lab))
Error                    Var(Error)
Corrected Total          .
         Type 1 Estimates
Variance Component          Estimate
Var(Lab)                     0.06017
Var(Bat(Lab))              0.0053681
Var(Error)                 0.0062972
```

Analysis of lab data

```
> library(MASS)
> Lab <- rep(1:6, rep(6,6))
> Bat <- rep(rep(1:3, rep(2,3)), 6)
> Conc <- coop$Conc[coop$Spc=="S1"]

> pdf("lab.pdf", pointsize=9, width=4.5, height=3.5)
> a <- order(sapply(split(Conc, Lab), mean))
> x <- rep(a,6)
> plot(Conc, x, type="n", ylab="Lab", yaxt="n",ylim=c(0.5,6.5))
> axis(side=2, at=1:6, labels=a)
> for (i in 1:6) {
  abline(i, 0, lty=3)
  points(Conc[Lab==a[i]], rep(i,6),
         pch=as.character(Bat[Lab==a[i]]),
         col=Bat[Lab==a[i]], cex=.8)
}
> dev.off()
```

Analysis of the lab data



Common features

- The levels of the some factors are chosen at random from a well-defined population of factor levels. We are interested in drawing inference about the general population using information from these observed (chosen) levels.
- There exists certain groups (clusters) in the data. For example, for the personnel example, ratings from the same officer form a group. Responses within the same group could be correlated.
- There could be different groups at different levels. For example, for the lab example, concentrations from the same laboratory form a group, and concentrations from the same batch form a smaller group nested within a laboratory.
- Responses within the same group could be correlated. Random effects associated with groups introduce correlations.

Summary

- The classical ANOVA approaches have difficulty handling more complex data (e.g., unbalanced designs, repeated measures, etc.). They do not model the covariance stucture directly.
- In 220A, we learned theory and inference methods for the general linear models that apply to regression, ANOVA, and ANCOVA models. Linear models are used to model the mean structure.
- We now learn theory and inference methods for the general linear mixed effects models, which apply to the classical random and mixed effects models, and many other models. Linear mixed effects models are used to model both the mean and covariance structure.