Analysis of Variance

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ANALYSIS OF VARIANCE

Examples: Data on blood pressure reductions for patients receiving 3 different drugs.

- Six patients randomized to each drug
- Sitting diastolic pressure measured before randomization (baseline) and after 4 weeks of treatment.

Drug 1: 10, 11, 15, 11, 12, 37

Drug 2: 8, 7, 8, 10, 12, 11

Drug 3: 7, 9, 11, 9, 4, 2

One-Way ANOVA

- Data: $Y_{ij}, i = 1, \cdots, I; j = 1, \cdots, n_i$

Y_{ij} is distributed normally with mean μ_i, and constant variance

Wish to test:

$$H_0 : \mu_1 = \cdots = \mu_I$$

against the alternative $H_1 : \mu_i \neq \mu_j$ for at least one pair $(i, j), i \neq j$.

One approach to model the data is to use the following formulation,

$$Y_{ij} = \mu_i + \epsilon_{ij}$$

Under the normality assumption, the maximum likelihood estimators of the means are given by

$$\hat{\mu}_i = \frac{\Sigma_j Y_{ij}}{n_i}$$

which also correspond to the OLS estimators obtained by minmizing

$$\sum_{ij}(Y_{ij} - \mu_i)^2$$

Decompose total sum of squares (SST) into diff sources of variation:

- Between samples (SSTrt)
- Within sample (SSE)

$$\sum_i \sum_j (Y_{ij} - \bar{Y}_{..})^2 = \sum_i n_i (Y_{i.} - \bar{Y}_{..})^2 + \sum_{ij} (Y_{ij} - \bar{Y}_{i.})^2$$

One-Way ANOVA Table

Source of Variation	df	Sum of Squares	Mean Squares
Treatment	I-1	SSTrt	SSTrt/(I-1)
Error	N-I	SSE	SSE/N-I
Total	N-1	SST	

A test statistic for H_o may be constructed based on the ratio

$$F = MSTrt/MSE$$

which, under H_o and model assumptions, has an $F_{I-1,N-I}$ distribution, where $N = \Sigma_i n_i$.

Implementation

R: aov() or glm()

SAS: PROC ANOVA, PROC GLM, and PROC MIXED.

> anov1 <- aov(Y~drug)
> summary(anov1)

	Df	SS	MSq	F Value	Pr(F)
drug	2	261.8	130.9	3.16	0.072
Residuals	15	621.3	41.4		

If $\bar{Y}_{i.}$ has a normal distribution with mean μ_i and variance σ^2/n_i,

$$\frac{n_i(\bar{Y}_{i.} - \mu_i)}{\sqrt{MSE}}$$

has a t-distribution with N-I degrees of freedom. This result may be used to construct confidence interval for μ_i or the difference between two means $\mu_i - \mu_j$.

For the latter:

a $100(1-\alpha)\%$ confidence interval is given by

$$D_{12} \pm t_{\alpha/2,N-I}\sqrt{MSE(1/n_i + 1/n_j)}$$

$$D_{ij} = \bar{Y}_{i.} - \bar{Y}_{j.}$$

- Suppose Ho is rejected,

$$H_0 : \mu_1 = \cdots = \mu_I$$

Interested in determining which means are different from which other ones.

If there are g > 2 comparisons, the probability that at least one interval not including the true difference is no longer α.

Assuming independence, the probability that at least one of the *k* comparisons will reject a true null hypothesis $= 1 - (1 - \alpha)^k$

k	1	2	3	4	5	…	10
α_E	0.05	0.10	0.14	0.19	0.23	…	0.40

For *k* = 10 comparisons, there is a 40% chance that we will reject erroneously at least one true null hypothesis!

Goal: construct simultaneous confidence intervals, such that the joint or simultaneous level is at least the desired level, 1 - α

Bonferroni Method

Given g pairs of comparisons, the Bonferroni method constructs confidence intervals, each at level $\alpha' = \alpha/g$.

$$D_{ij} \pm t_{\alpha'/2,N-I}\sqrt{MSE(1/n_i + 1/n_j)}$$

Then the coverage probability of the joint or simultaneous confidence intervals is at least $1 - \alpha$.

Tukey Method

$$D_{ij} \pm Q^{\alpha}_{I,N-I}\sqrt{MSE(1/n_i + 1/n_j)}$$

where $Q^{\alpha}_{I,N-I}$ is the critical point of a Studentized range distribution with I means and N-I error degrees of freedom.

Scheffe Intervals

A procedure that results in wider intervals than the Tukey intervals, but with correct coverage, is given by

$$D_{ij} \pm \sqrt{(I-1)F_{\alpha,I,N-I}}\sqrt{MSE(1/n_i + 1/n_j)}$$

Fisher's Least Significant Difference

A procedure that is often used for pre-defined comparisons, is

$$D_{ij} \pm F_{\alpha,I,N-I}\sqrt{MSE(1/n_i + 1/n_j)}$$

This procedure does not control the experiment-wise error rate, and results in narrow confidence intervals.

Dunnett's Procedure

When interest lies in comparing I-1 groups against a reference group:

$$D_{ij} \pm d^{\alpha}_{I,N-I}\sqrt{MSE(1/n_i + 1/n_j)}$$

Reading Assignment. For p-values:

```
help(p.adjust)
 p.adjust(p, method = p.adjust.methods)
p.adjust.methods
    # c("holm", "hochberg", "hommel", "bonferroni",… "fdr", "none")
help(pairwise.t.test)
```

Departures From Assumptions

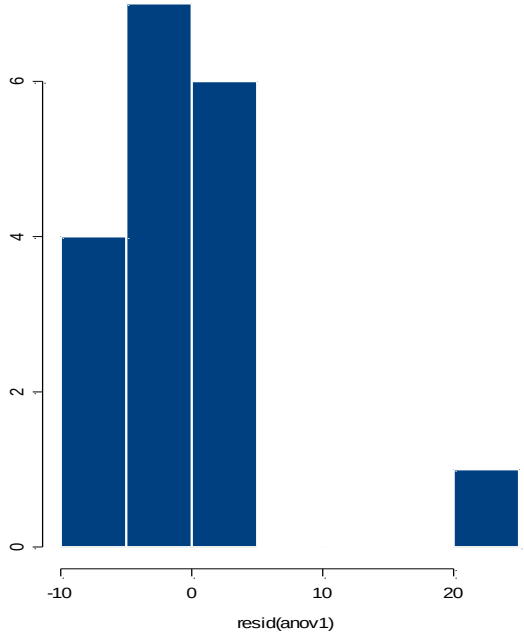
Non-normality

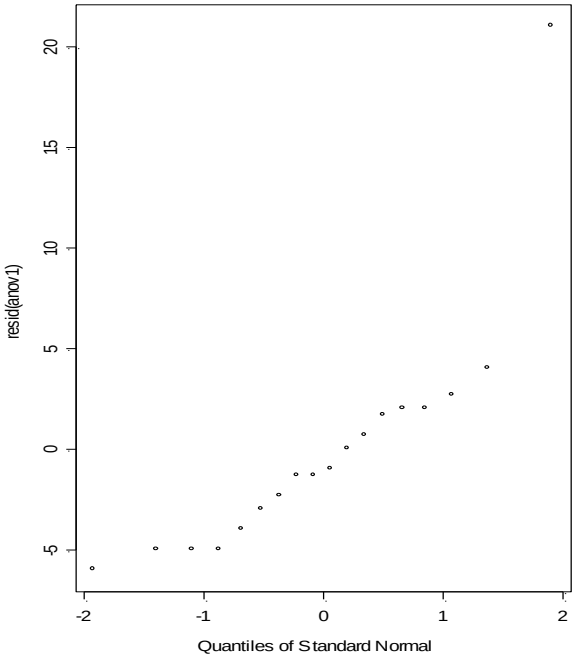
- Validity of the p-values suspect in small samples.
- For large samples, the F-test is generally Robust
- Accompanying loss in efficiency may be substantial
- Confidence intervals will not be accurate

Detection:

- Residual analysis: qqnorm, histograms, etc.

- hist(resid(anov1));
- qqnorm(resid(anov1)





Measures against *Non-normality:*

- Transformations: Box-Cox

$$y(\lambda) = \begin{cases} \frac{y^\lambda - 1}{\lambda}, & \text{if } \lambda \neq 0; \\ \log y, & \text{if } \lambda = 0. \end{cases}$$

Alternatively, one may use nonparametric or robust procedures.

The Kruskal-Wallis test

- A generalization of the Wilcoxon rank-sum test, when there are more than two groups.
- Based on the joint ranks of the observations (i.e., ranked from 1 to N= $\Sigma_{i=1}^{I} n_1$

•Let R_i. = mean of ranks for i'th group
•R.. be the overall mean rank.
•Then assuming no ties:

$$T_{KW} = \frac{12}{N(N+1)} \sum_{i=1}^{I} n_i (\bar{R}_{i.} - R_{..})^2$$

which under $H_0 : \mu_1 = \cdots = \mu_I$ has an approximate χ^2_{I-1} distribution.

Remarks:

- Approximation is good provided $n_i > 5$
- If there are ties, appropriate correction factors must be used. (Reading Assignment)
- Kruskal-Wallis test assumes ordinal or numeric data
- Also assumes the shapes of the I distributions are the same.

One also may perform multiple comparisons using the following:

$$\bar{R}_{i.} - \bar{R}_{k.} \pm Z_{1-\alpha/2g}\left[\frac{N(N+1)}{12}(1/n_i + 1/n_k)\right]^{1/2}$$

> kruskal.test(Y,drug)

Kruskal-Wallis rank sum test

data: Y and drug

Kruskal-Wallis chi-square = 7.9476, df = 2, p-value = 0.0188

alternative hypothesis: two.sided

Departures From Assumptions

Unequal Variances

- p-values may not be reliable.

effect is mor serious if the large σ_i is associated with the samller n_i's. This typically leads to more frequent false rejections.

Test for homogeneity of variances:

- Bartlett's test
- Levene's test
- Box's test
- Hartley's max test

Bartlett's test

$$T = c^{-1}(\nu ln(\hat{\sigma}^2) - \sum_i \nu_i ln(\hat{\sigma}_i^2)$$

where $\nu_i = n_i - 1$, $\nu = \Sigma_i \nu_i$, and

$$c = 1 + \frac{1}{3(I-1)}(\sum_i \nu_i^{-1} - \nu^{-1})$$

and $\hat{\sigma}_i$ and $\hat{\sigma}$ are the i'th sample and pooled variances. The test rejects when $T > \chi^2_{I-1}$.

The test is highly dependent on normality assumption.

Two-Way ANOVA

In many applications, one-way ANOVA may not be adequate.

Examples: Data on blood pressure reductions for patients receiving 3 different drugs (cont'd)

Male	Female:
Drug 1: 11, 15, 11,	Drug 1: 10, 12, 37
Drug 2: 8, 7, 8	Drug 2: 10, 12, 11
Drug 3: 7, 9, 11	Drug 3: 9, 4, 2

Two-Way ANOVA

A second variable included in a model to:

- Improve precision
- Reduce dependence within the levels of a factor of interest
- Reduce bias arising as a result of confounding

When the stratification variable is numeric, Analysis of Covariance (ANCOVA).

•When the variable is a factor with two or more levels, two-way ANOVA.

Two-Way ANOVA

ANOVA model is given by:

$$Y_{ijk} = \mu_{ij} + \epsilon_{ijk}$$

where $i = 1, \cdots, I, j = 1, \cdots, J, k = 1, \cdots, n_{ij}$, and ϵ_{ijk} are typically assumed to be i.i.d. $N(0, \sigma^2)$.

OLS estimator:

$$\hat{\mu}_{ij} = \bar{Y}_{ij\cdot}$$

It is often more convenient to use the following alternative formulation

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \gamma_{ij} + \epsilon_{ijk}$$

When the design is balanced, i.e., all $n_{ij} = n$, the least squares estimators of the unknown parameters are given as follows:

$$\hat{\mu} = \bar{Y}_{...}$$

$$\hat{\alpha}_i = \bar{Y}_{i..} - \bar{Y}_{...}$$

$$\hat{\beta}_j = \bar{Y}_{.j.} - \bar{Y}_{...}$$

$$\hat{\gamma}_{ij} = \bar{Y}_{ij.} - \bar{Y}_{i..} - \bar{Y}_{.j.} + \bar{Y}_{...}$$

Decomposition of SST for balanced 2-way designs:

$$SSA = nJ \sum_{i=1}^{I} (\bar{Y}_{i..} - \bar{Y}_{...})^2$$

$$SSB = nJ \sum_{j=1}^{J} (\bar{Y}_{.j.} - \bar{Y}_{...})^2$$

$$SSAB = n \sum_{i=1}^{I} \sum_{j=1}^{J} (\bar{Y}_{ij.} - \bar{Y}_{i..} - \bar{Y}_{.j.} + \bar{Y}_{...})^2$$

$$SSE = \sum_{ijk} (Y_{ijk} - \hat{Y}_{ij.})^2$$

Two-Way ANOVA Table: Balanced Design

Source	df	SS	MS
A	I-1	SSA	MSA=SSA/(I-1)
B	J-1	SSB	MSB=SSB/(J-1)
AB	(I-1)(J-1)	SSAB	MSAB/(I-1)(J-1)
Error	IJ(n-1)	SSE	SSE/IJ(n-1)
Total	IJN-1	SST	

hypothesis of no treatment effect,

$$H_0 : \alpha_1 = \cdots = \alpha_I$$

the normal-model test statistic is given by

$$F = \frac{MSA}{MSE}$$

which under H_o has an $F_{I-1,IJ(n-1)}$ distribution.

When there is no significant interaction, it is often advisable to work with the reduced model,

$$Y_{ijk} = \mu + \alpha_i + \beta_j + \epsilon_{ijk}$$

Advantages of additive model formulation:

- More error degrees of freedom is obtained, giving more powerful F tests for the main effects.

- Estimation of main effect parameters straightforward even when the design is unbalanced or some cells are empty .

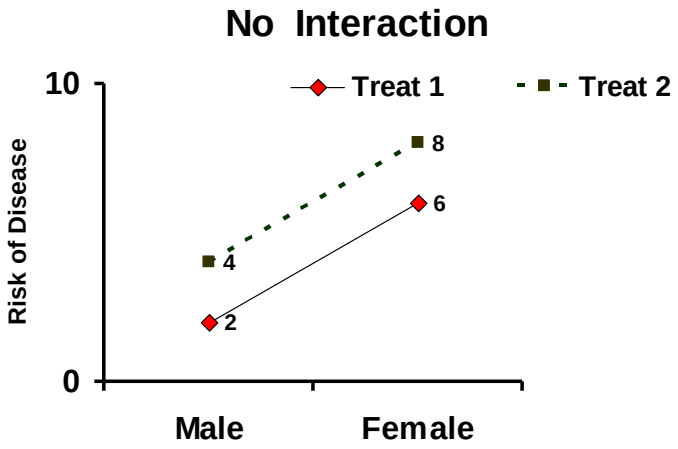
$$\hat{\mu}_{ij} = \hat{\mu} + \hat{\alpha}_i + \hat{\beta}_j$$

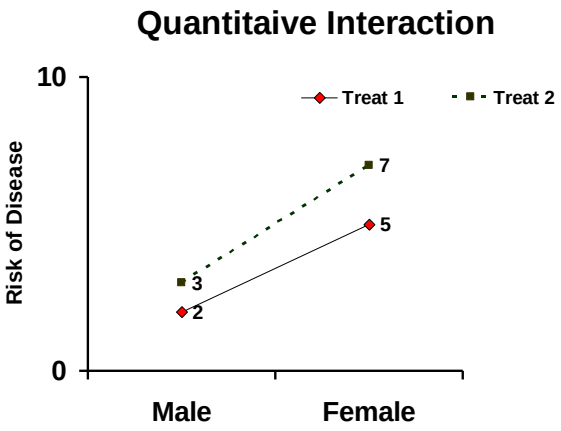
so that the i'th marginal mean is estimated by

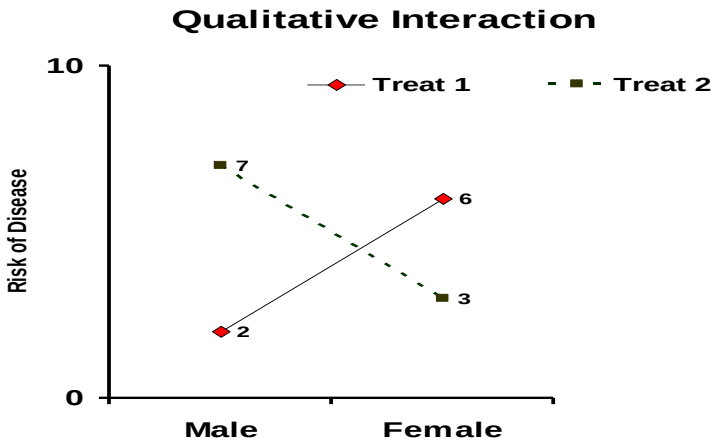
$$\hat{\mu}_{i.} = \frac{\Sigma_{j=1}^{J} \hat{\mu}_{ij}}{J}$$

When the interaction term is significant:

- Evaluate the nature and strength of the interaction.

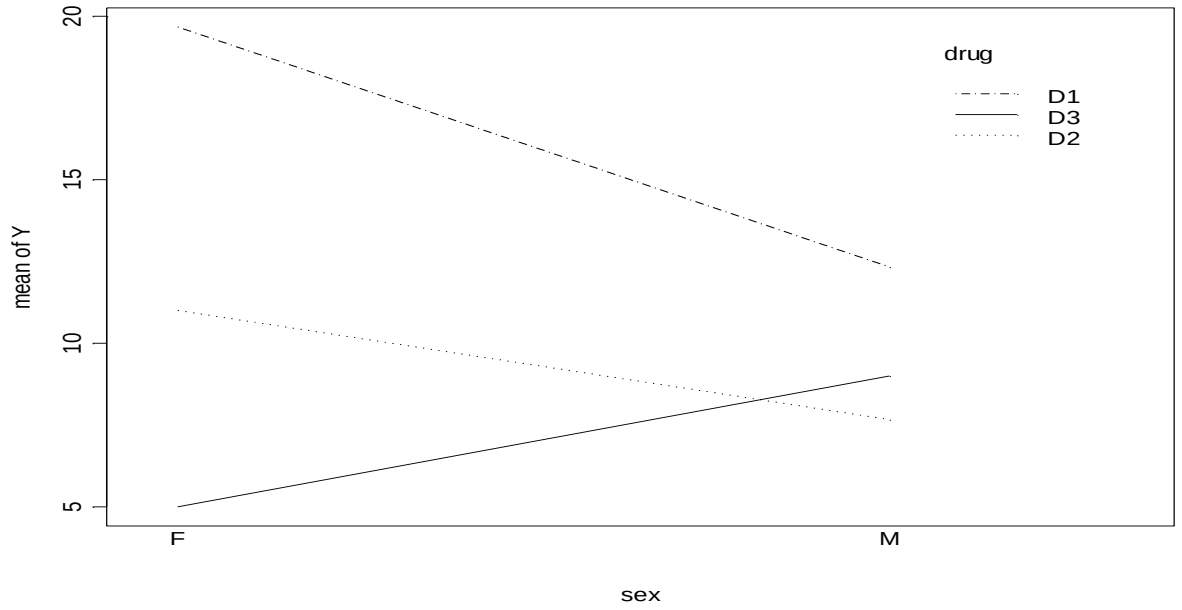






When the interaction term is significant:

- Evaluate the nature and strength of the interaction.
  - Commonly used test to determine whether the interaction qualitative or quantitative: Gail-Simon test
    [Biometrics. Vol. 41 No. 2 (June 1985): 361-372]
  - Plot using interaction.plot(block,trt,Y)



```
> fit2way <- aov(Y~drug*sex)
> summary(fit2way)
             Df   SSq      Mean Sq    F Value    Pr(F)
     drug    2   261.78    130.89     3.14         0.08
      sex    1   22.22     22.22      0.53         0.48
 drug:sex    2   99.11     49.56      1.19         0.34
Residuals   12   500.0     41.67
```

The Friedman rank-sum test

- Assumes a randomized block design without replication

$$Y_{ij} = \mu + \alpha_i + \beta_j + \epsilon_{ij}$$

and the null hypothesis of interest

$$H_o : \alpha_1 = \cdots = \alpha_I$$

Within each block (ie., $j = 1, \cdots, J$), rank the observations separately from 1 to I. Let $\bar{R}_{i.}$ be the mean rank for the observations in the i'th group. Then under H_0, $\bar{R}_{1.} \approx \cdots \approx \bar{R}_{I.}$.

$$F = \frac{12J}{I(I+1)} \sum_{i=1}^{I} (\bar{R}_{i.} - \bar{R}_{..})^2$$

which, under H_0, is approximately χ^2_{I-1}.

Implementation:
friedman.test(Y,groups,blocks)
SAS: PROC FREQ.

```
> tapply(Y,list(sex,drug),mean)
     D1   D2 D3
F  19.7 11.0  5
M  12.3  7.7  9
```

```
> Ymean <- c(19.7,12.3,11,7.7,5,9)
> Drug <-rep(c("D1","D2","D3"),c(2,2,2))
> Sex <-c("F","M","F","M","F","M")
> Drug <-factor(Drug)
> Sex <-factor(Sex)
```

```
> friedman.test(Ymean,Drug,Sex)

        Friedman rank sum test

data:  Ymean and Drug and Sex
Friedman chi-square = 3, df = 2, p-value = 0.2231
alternative hypothesis: two.sided
```

Other tests in PROC FREQ

- The Van Elteren test

Example

Data on **Blood Pressure** reduction (Y), **Baseline Blood Pressure (Base)** and Treatment (trt)

ID	Y	Base	trt
1	7.1	61	Drug
2	6.6	56	Drug
3	7.8	58	Drug
4	6.8	68	Drug
5	9.4	64	Drug
6	9.7	57	Drug
7	8.5	55	Drug
8	9.9	59	Drug
9	6.1	51	Drug
10	8.0	60	Drug
11	8.8	88	Placebo
12	8.5	85	Placebo
13	8.1	81	Placebo
14	8.9	89	Placebo
15	8.7	87	Placebo
16	8.4	84	Placebo
17	8.1	81	Placebo
18	7.8	78	Placebo
8.1	81	Placeb	
20	8.5	85	Placebo

One-Way ANOVA:

> summary(aov(Y ~ trt))

	Df	SS	MeanSq	F	Pr(F)
trt	1	0.42	0.42	0.60	**0.450**
Resid	18	12.68	0.70		

	Base Mean	**Y Mean**
Drug	59.7	8.07
Placebo	83.6	8.34

Analysis of Covariance
ANCOVA

Example: Subjects randomized to Drug or Placebo.

Data on **Blood Pressure** reduction (Y) after 4 weeks of treatment,

Baseline Blood Pressure (Base)

Ho: No Difference in Mean BP Reduction (Y) for Drug & Placebo

ID	Y	Base	trt
1	7.1	61	Drug
2	6.6	56	Drug
3	7.8	58	Drug
4	6.8	68	Drug
5	9.4	64	Drug
6	9.7	57	Drug
7	8.5	55	Drug
8	9.9	59	Drug
9	6.1	51	Drug
10	8.0	60	Drug
11	8.8	88	Placebo
12	8.5	85	Placebo
13	8.1	81	Placebo
14	8.9	89	Placebo
15	8.7	87	Placebo
16	8.4	84	Placebo
17	8.1	81	Placebo
18	7.8	78	Placebo
19	8.1	81	Placebo
20	8.5	85	Placebo

One-Way ANOVA:

> summary(aov(Y ~ trt))

	Df	SS	MeanSq	F	Pr(F)
trt	1	0.42	0.42	0.60	**0.450**
Resid	18	12.68	0.70		

	Base Mean	**Y Mean**
Drug	59.7	8.07
Placebo	83.6	8.34

Regression Effect

Regression to the Mean

Suppose X_{ij} is a covariate of interest, and consider the ANOCVA model

$$Y_{ij} = \mu_i + \beta X_{ij} + \epsilon_{ij}$$

Note that

$$\bar{Y}_{i.} \approx \hat{\mu}_i + \beta \bar{X}_{i.}$$

Thus, comparing μ_i and μ_k based on $\bar{Y}_{i.} - \bar{Y}_{k.}$ would be inappropriate unless $\bar{X}_{i.} = \bar{X}_{k.}$. So , comparison is generally performed at a common value of X, say $\bar{X}_{..}$. For convenience, let

$$Y_{ij} = \mu_i + \beta(X_{ij} - \bar{X}_{..}) + \epsilon_{ij}$$

Adjusted mean (a.k.a. LS Mean)

$$\hat{\mu}_i = \hat{Y}_{i.} - \hat{\beta}(\bar{X}_{i.} - \bar{X}_{..})$$

In the above

$$\hat{\beta} = \frac{\Sigma_{i=1}^{I} \Sigma_{j=1}^{n_i} (y_{ij} - \bar{Y}_{i.})(X_{ij} - \bar{X}_{i.})}{\Sigma_{i=1}^{I} \Sigma_{j=1}^{n_i} (X_{ij} - \bar{X}_{i.})^2}$$

$$\hat{\sigma}^2 = \frac{1}{N - I - 1} \sum_{ij} (Y_{ij} - \hat{\mu}_{i.} - \hat{\beta}(\bar{X}_{i.} - \bar{X}_{..}))^2$$

$$var(\hat{\beta}) = \frac{\sigma^2}{\Sigma_{i=1}^{I} \Sigma_{j=1}^{n_i} (X_{ij} - \bar{X}_{i.})^2}$$

One-Way ANOVA:

> summary(aov(Y ~ trt))

	Df	SS	MeanSq	F	Pr(F)
trt	1	0.42	0.42	0.60	**0.450**
Resid	18	12.68	0.70		

ANCOVA

> summary(aov(Y ~ Base+trt))

	Df	SS	MeanSq	F	Pr(F)
Base	1	2.40	2.40	5.9	0.026
trt	1	3.81	3.81	9.41	**0.007**
Resid	17	6.89	0.41		

	Base	**Y**	**LSM**
Drug	59.7	8.07	9.3
Placebo	83.6	8.34	7.1

Nonparallel Regression Lines

Suppose now that

$$Y_{ij} = \mu_i + \beta_i(X_{ij} - \bar{X}_{\cdot\cdot}) + \epsilon_{ij}$$

The above arises when the marginal mean differences are different for different values of X_{ij} .

- In the blood pressure example, patients may respond differently to different drugs depending on the values of their baseline blood pressure.

When the lines are not parallel, different lines have to be fitted for each i.

$$\hat{\beta}_i = \frac{\Sigma_{j=1}^{n_i}(y_{ij} - \bar{Y}_{i.})(X_{ij} - \bar{X}_{i.})}{\Sigma_{j=1}^{n_i}(X_{ij} - \bar{X}_{i.})^2}$$

giving

$$\hat{\mu}_i = \hat{Y}_{i.} - \hat{\beta}_i(\bar{X}_{i.} - \bar{X}_{..})$$

A test for parallelism may be performed by testing for the significance of treatment-by-covariate interaction

$$H_0 : \beta_1 = \cdots \beta_I$$

The test statistic is given by

$$\frac{\Sigma_{i=1}^{I}(\hat{\beta}_i - \hat{\beta})^2 \, \Sigma_j (X_{ij} - \bar{X}_{i.})^2}{(I-1)\hat{\sigma}^2}$$

which under H_0 has an $F_{I-1,N-2I}$ distribution.

In the above

$$\hat{\beta} = \frac{\Sigma_{i=1}^{I} \, \Sigma_{j=1}^{n_i} (Y_{ij} - \bar{Y}_{i.})(X_{ij} - \bar{X}_{i.})}{\Sigma_{i=1}^{I} \, \Sigma_{j=1}^{n_i} (X_{ij} - \bar{X}_{i.})^2}$$

Test for Parallelism

```
> summary(aov(Y ~  Base*trt))
            Df  SS   MeanSq  F      Pr(F)
Base     1  2.401  2.40     5.590    0.031
   trt      1  3.814  3.81     8.88     0.009
Base:trt  1  0.017  0.017  0.04     0.840
```

When Ho is rejected, inference about the marginal mean differences must be performed for each X = x

$)^2$

Remarks:

For non-normal data, use rank-based ANCOVA:

- Iman and Conover: Ranks are substituted for Y and X, if both random
- Stephen and Jacobson: Transform only Y, if X is fixed (e.g., X=Age).

Other ANOVA Models

Example 1. Study on effects of teaching methods on student performance. All 5 teachers in a given school (i.e., 5 different methods) included in a study, each assigned 10 students at random. At the end of a training period, scores on a standardized test recorded.

Example 2. In another school there are 100 teachers. 5 teachers chosen at random (i.e., 5 different methods), and each assigned 10 students at random. At the end of a training period, scores on a standardized test recorded.

NB: The first school corresponds to Fixed Effects ANOVA (Model I), since all the levels of the factor "Teacher" are in the study.

The levels of the factor "Teacher" in the second case are random. Corresponds to Random Effects ANOVA (Model II)

One Way Random Effects ANOVA Model (Model II)

$$Y_{ij} = \mu_i + \epsilon_{ij}$$

where μ_i are iid $N(\mu, \sigma_A^2)$, ϵ_{ij} are also iid $N(0, \sigma_e)$, and independent of μ_i. Note that if all teachers teach the same way, $\mu_i = \mu$, and hence $\sigma_A^2 = 0$.

A test for treatment difference may then be formulated in term sof

$$H_0 : \sigma_A^2 = 0$$

vs

$$H_1 : \sigma_A^2 > 0$$

Total sum of squares (SST) decomposed:

- Sum of squares due to treatment (SSA)+
- Error sum of squares (SSE), where

$$SSA = \sum_i n_i(\bar{Y}_{i.} - \bar{Y}_{..})^2$$

$$SSE = \sum_i \sum_j (Y_{ij} - \bar{Y}_{i.})^2$$

Assuming all $n_i = n$, it can also be shown that,

$$E[MSA] = E[SSA/(I-1)] = n\sigma_A^2 + \sigma_e^2.$$

$$E(MSE) = \sigma_e^2.$$

To test

$$H_0 : \sigma_A^2 = 0$$

vs

$$H_1 : \sigma_A^2 > 0$$

$$F = \frac{MSA}{MSE}$$

which under H_o has an $F_{I-1,N-I}$ distribution

Remark: In the One-way case, the test similar to that of Fixed Effects model

Reading assignment: Confidence intervals for σ_A^2 and $\frac{\sigma_A^2}{\sigma_A^2 + \sigma_e^2}$

Two-Factor Models: Model II

$$Y_{ijk} = \mu + a_i + b_j + (ab)_{ij} + \epsilon_{ijk}$$

where $i = 1, \cdots, I; j = 1, \cdots, J; k = 1, \cdots, n_{ij}$; $a_i, b_j, (ab)_{ij}, \epsilon_{ijk}$ are mutually independent normal random variables, with mean 0, and respective variances: $\sigma_A^2, \sigma_B^2, \sigma_{AB}^2, \sigma_e^2$.

When the design is balanced, we have

$$SST = SSA + SSB + SSAB + SSE$$

where

$$SSA = nJ \sum_i (\bar{Y}_{i..} - \bar{Y}_{..})^2$$

$$SSB = nI \sum_j (\bar{Y}_{.j.} - \bar{Y}_{..})^2$$

$$SSAB = n \sum_{ij} (\bar{Y}_{ij.} - \bar{Y}_{i..} - \bar{Y}_{.j.} + \bar{Y}_{..})^2$$

$$SSE = \sum_{ijk} (Y_{ijk} - \bar{Y}_{ij.})^2$$

and

$$SST = \sum_{ijk} (Y_{ijk} - \bar{Y}_{..})^2$$

$$E(MSA) = \sigma_e^2 + n\sigma_{AB}^2 + nJ\sigma_A^2$$

$$E(MSB) = \sigma_e^2 + n\sigma_{AB}^2 + NI\sigma_B^2$$

$$E(MSAB) = \sigma_e^2 + n\sigma_{AB}^2$$

and

$$E(MSE) = \sigma_e^2$$

Two-Way Random Effects Model ANOVA Table

Source	df	SS	MS	EMS
A	I-1	SSA	SSA/(I-1)	$\sigma_e^2 + n\sigma_{AB}^2 + nJ\sigma_A^2$
B	J-1	SSB	SSB/(J-1)	$\sigma_e^2 + n\sigma_{AB}^2 + nI\sigma_B^2$
AB	(I-1)(J-1)	SSAB	SSAB/(I-1)(J-1)	$\sigma_e^2 + n\sigma_{AB}^2$
Error	(n-1)IJ	SSE	SSE /(n-1)IJ	σ_e^2
TOTAL	N-1	SST		

Mixed Effects Models: Model III

Example: Suppose three treatments are to be compared.

- 5 hospitals selected at random from a district of 100 hospitals
- 5 patients are randomly assigned to each treatment in each hospital

•The factor "treatment" is fixed, since all the levels are included in the study.

•“Hospital” is random, since the levels are a random sample.

Two-way Mixed Effects Model

$$Y_{ijk} = \mu + \alpha_i + b_j + (\alpha b)_{ij} + \epsilon_{ijk}$$

where μ and α_i are constant,

$$b_j \sim N(\mu, \sigma_b^2)$$

$$(\alpha b)_{ij} \sim N(0, \frac{(I-1)}{I}\sigma_{AB}^2),$$

ϵ_{ijk} is $N(0, \sigma_e^2)$, and all the random quantities are mutually independent.

Two -Way Mixed Effects ANOVA Table

Source	df	SS	MS	EMS
A (Fixed)	I-1	SSA	SSA/(I-1)	$\sigma_e^2 + \frac{nJ}{J-1}\sum_i \alpha_i^2 + n\sigma_{AB}^2$
B (Random)	J-1	SSB	SSB/(J-1)	$\sigma_e^2 + nI\sigma_B^2$
AB (Random)	(I-1)(J-1)	SSAB	SSAB/(I-1)(J-1)	$\sigma_e^2 + n\sigma_{AB}^2$
Error (Random)	(n-1)IJ	SSE	SSE /(n-1)IJ	σ_e^2
TOTAL	N-1	SST		

Inference about the fixed effect (A)

$$H_0 : \alpha_i = 0$$

$$F = \frac{MSA}{MSAB}$$

which under H_o has an $F_{I-1,(I-1)(J-1)}$ distribution

Two - Way Mixed Effects ANOVA Table: Balanced Design

Source	df	SS	MS	EMS
A (Fixed)	I-1	SSA	SSA/(I-1)	$\sigma_e^2 + \frac{nJ}{J-1}\sum_i \alpha_i^2 + n\sigma_{AB}^2$
B (Random)	J-1	SSB	SSB/(J-1)	$\sigma_e^2 + nI\sigma_B^2$
AB (Random)	(I-1)(J-1)	SSAB	SSAB/(I-1)(J-1)	$\sigma_e^2 + n\sigma_{AB}^2$
Error (Random)	(n-1)IJ	SSE	SSE /(n-1)IJ	σ_e^2
TOTAL	N-1	SST		

If the interaction term is not significant, then an appropriate test statistic, based on the reduced model, is

$$F = \frac{MSA}{MSAB + MSE}$$

Null distribution?

Inference about the random effect (B)

$$H_0 : \beta_j = 0$$

Two - Way Mixed Effects ANOVA Table: Balanced Design

Source	df	SS	MS	EMS
A (Fixed)	I-1	SSA	SSA/(I-1)	$\sigma_e^2 + \frac{nJ}{I-1}\sum_i \alpha_i^2 + n\sigma_{AB}^2$
B (Random)	J-1	SSB	SSB/(J-1)	$\sigma_e^2 + nI\sigma_B^2$
AB (Random)	(I-1)(J-1)	SSAB	SSAB/(I-1)(J-1)	$\sigma_e^2 + n\sigma_{AB}^2$
Error (Random)	(n-1)IJ	SSE	SSE /(n-1)IJ	σ_e^2
TOTAL	N-1	SST		

$$F = \frac{MSB}{MSE}$$

which under H_o has an $F_{I-1,(n-1)IJ}$ distribution

Example. Consider a study comparing 3 teaching methods.

- A random sample of 5 schools selected
- From each school 3 teachers randomly chosen.
  - Each teacher was then assigned a teaching method at random and asked to apply it in their class of about 20 students each.
- The scores (Y_{ij}) of each student were then recorded at the end of the semester.

In this example, each level of the factor "teacher" occurs with only one level of "school", and each of the 15 levels is meaningful only given the level of "school". The factor "teacher" is said to be *nested* within "school".

Two-Way Nested Designs

When both factors are random,

$$Y_{ijk} = \mu + a_i + b_{j(i)} + \epsilon_{ijk}$$

where $b_{j(i)}$ denotes the effect of B at the j'th level, when A is at the i'th level. Further a_i, $b_{j(i)}$ and ϵ_{ijk} are mutually independent normal

random variables, with mean 0 and, respective variances:

$$\sigma_A^2,\ \sigma_{B(A)}^2 \text{ and } \sigma_e^2$$

For the balanced case, the sums of squares are given by:

$$SSA = Jn \sum_i (\bar{Y}_{i..} - \bar{Y}_{...})^2$$

$$SSB(A) = n \sum_{ij} (\bar{Y}_{ij.} - \bar{Y}_{i..})^2$$

$$SSE = \sum_{ijk} (\bar{Y}_{ijk} - \bar{Y}_{ij.})^2$$

Two -Way Nested Random Effects ANOVA Table

Source	df	SS	MS	EMS
A (Random)	I-1	SSA	SSA/(I-1)	$\sigma_e^2 + nJ\sigma_A^2 + n\sigma_{B(A)}^2$
B(A) (Random)	I(J-1)	SSB(A)	SSB(A)/I(J-1)	$\sigma_e^2 + n\sigma_{B(A)}^2$
Error (Random)	(n-1)IJ	SSE	SSE /(n-1)IJ	σ_e^2
TOTAL	N-1	SST		

When A is fixed and B is random, and B(A):

Source	df	SS	MS	EMS
A (Fixed)	I-1	SSA	SSA/(I-1)	$\sigma_e^2 + nJ\frac{Jn}{I-1}\sum_i \alpha_i^2$
B(A) (Random)	I(J-1)	SSB(A)	SSB(A)/I(J-1)	$\sigma_e^2 + \frac{n}{I(n-1)}\sum_{ij} \beta_{j(i)}^2$
Error (Random)	(n-1)IJ	SSE	SSE /(n-1)IJ	σ_e^2
TOTAL	N-1	SST		

Repeated Measures Design

Example. Consider a clinical trial comparing three treatment groups. Subjects were randomized to each treatment, and measurements were taken at weekly.

Observation taken over time on the same subject may be correlated.

- The usual ANOVA will not be applicable to this case.

Repeated Measures Design

Let Y_{ijk} denot the measurement on the k'th subject, assigned to treatment i, and taken at time j.

$$Y_{ijk} = \mu + \alpha_i + \tau_j + (\alpha\tau)_{ij} + S(\alpha)_{k(i)} + \epsilon_{ijk}$$

where α_i is the i'th treatment effect, τ is time effect, and $S(\alpha)$ stands for subject nested in treatment.

Since the error terms may be correlated, several correlation structures may be possible:

- Compound symmetry (i.e., equal correlations)

$$Corr(Y_{ijk}, Y_{ilk}) = \rho, \ \forall j \neq l$$

- AR(1)
- Unstructured

The following is a decomposition of the Total Sum of Squares (SST)

$$SSTreatment = J \sum_i n_i (\bar{Y}_{i..} - \bar{Y}_{...})^2$$

$$SSTime = n_+ \sum_j (\bar{Y}_{.j.} - \bar{Y}_{...})^2$$

$$SSTreat*Time = \sum_{i,j} n_i (\bar{Y}_{ij.} - \bar{Y}_{i..} - \bar{Y}_{.j.} + \bar{Y}_{...})^2$$

$$SSS(Treat) = J \sum_{i,k} n_i (\bar{Y}_{i.k} - \bar{Y}_{i..})^2$$

$$SSE = \sum_{ijk} (Y_{ijk} - \bar{Y}_{i.k} - \bar{Y}_{ij.} + \bar{Y}_{i..})^2$$

$$SST = \sum_{i,j,k} (Y_{ijk} - \bar{Y}_{i..})^2$$

Repeated Measures ANOVA Table

Source	df	SS	F Statistic
Treatment	I-1	SS Treat	$\frac{MSTreat}{MS\ \ S(Treat)}$
Time	J-1	SS Time	$\frac{MSTime}{MSE}$
Treat*Time	(I-1)(J-1)	SS Time*Time	$\frac{MSTreat*Time}{MSE}$
S (Treat)	$\sum_i (n_i - 1) = n_+ - I$	SS S(Treat)	$\frac{MSS(Treat)}{MSE}$
Error	$(\sum_i n_i - J)(J-1)$	SSE	
Total	SST		

Remarks:

- $\frac{MSTime}{MSE}$ and $\frac{MSTreat*Time}{MSE}$ may not have an F distribution with the usual degrees of freedom. Indeed, actual significance may be less strong than given by table.

  Under certain conditions (Huynh & Feldt), the distributions are F (e.g., when the correlation structure is independent or exchangeable or AR(1).

- More generally, models that take into account the correlation structure must be used (SAS PROC MIXED).

Example: Repeated measures

Subjects randomized to either Group 1, 2 or 3.

For each subject, response measured at Time 1, 2 and 3, following randomization and treatment.

ID	Group	Time	Y
1	1	1	15
1	1	2	29
1	1	3	25
2	1	1	11
2	1	2	28
2	1	3	27
3	2	1	14
3	2	2	12
3	2	3	16
4	2	1	11
4	2	2	10
4	2	3	13
5	3	1	21
5	3	2	22
5	3	3	19
6	3	1	14
6	3	2	18
6	3	3	16
7	3	1	13
7	3	2	10
7	3	3	11

```
proc glm data=repeat;
class ID Group Time;
model Y=Group ID(Group)Time group*time/ss3;
test h=group e=id(group);
run;
```

Source	DF	SS3	MS	F	Pr > F
Group	2	303	152	50.50	<.0001
ID(Group)	4	143	35.7	11.90	0.0019
Time	2	105	52.6	17.53	0.0012
Group*Time	4	211.6	52.9	17.63	0.0005

Tests of Hypotheses Using the Type III MS for ID(Group) as an Error Term

Source	DF	Type III SS	MS	F Value	Pr > F
Group	2	303	152	4.24	0.1027

Reading Assignment :

SAS' PROC GLM gives Type I - Type III *SS*.

Example: Model Y= A+B+A*B

Type I *SS:* Order-dependent (hierarchical, sequential). Each effect is adjusted for all other effects that appear earlier (to the left) in the model, but not for any effects that appear later in the model.

Type II *SS* are the reduction in the *SSE* due to adding the effect to a model that contains all other effects except effects that contain the effect being tested

Types III *SS* are each adjusted for all other effects in the model, regardless of order.

```
proc glm data=repeat;
class ID Group Time;
model Y=Group ID(Group)Time group*time/ss1;
test h=group e=id(group);
run;
```

Source	DF	Type I SS	Mean Square	F Value	Pr > F
Group	2	302.9761905	151.4880952	50.50	<.0001
ID(Group)	4	142.8333333	35.7083333	11.90	0.0019
Time	2	80.3809524	40.1904762	13.40	0.0028
Group*Time	4	211.6190476	52.9047619	17.63	0.0005

Tests of Hypotheses Using the Type I MS for ID(Group) as an Error Term

Source	DF	Type I SS	Mean Square	F Value	Pr > F
Group	2	302.9761905	151.4880952	4.24	0.1027

Reading assignment:
Compare the above results with the results obtained using the R function
aov(Y ~ Group*Time+Error(ID))

```
proc mixed data=repeat;
class ID Group Time;
model Y=Group Time group*time;
repeated/type=cs subject=ID;
run;
```

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Group	2	4	4.24	0.1027
Time	2	8	17.53	0.0012
Group*Time	4	8	17.63	0.0005

Problem Set

Reading Assignment: Ramsey and Shafer; Chapters 5, 6,13

1. Consider the Duodenal Ulcer data given in Problem 25, Chapter 5.

    a) Using an appropriate ANOVA model, determine whether there is a significant difference among the group means. Use both an F test and simultaneous confidence interval procedures
    b) Assess the assumptions of the ANOVA model.
    c) Compare the results to those obtained using a non-parametric procedure.

2) Consider the IQ scores data of Display 13.24, problem 19, Chapter 13.

    a) Do problem 19
    b) Assess the validity of all assumptions.