

Fall 2010, STAT 430

Repeated Measures Designs

=====

ssh UserID@umeg.umd.edu, tap sas913, sas
https://www.statlab.umd.edu/sasdoc/sashtml/onldoc.htm

Subjects are measured at every level of a factor. For example, every subjects gets all possible treatments. Previously, every subjects received only one treatment. We'll make this clear in the following.

Ex1. One-Factor Repeated Experiment

Have 2 factors: SUBJECT and DRUG.

Each subjects is given all 4 treatments 1,2,3,4 for pain relief. Then the subject's pain tolerance is measured. Enough time is allowed to pass between treatments to prevent residual effects, and thus guarantee independence between measurements.

Subject	Drug1	Drug2	Drug3	Drug4	
1	5	9	6	11	
2	7	12	8	9	NOTE: ONE OBS/CELL
3	11	12	10	14	
4	3	8	5	8	

```
DATA PAIN;  
INPUT SUBJECT DRUG PAIN;  
1 1 5  
1 2 9  
1 3 6  
1 4 11  
2 1 7  
2 2 12  
2 3 8  
ETC.
```

Better way to read the data using a do loop.

```
OPTION PS=35 LS=70;
```

```
DATA PAIN;  
INPUT SUBJ @;  
DO DRUG=1 TO 4;  
INPUT PAIN @;  
OUTPUT;  
END;  
DATALINES;  
1 5 9 6 11  
2 7 12 8 9  
3 11 12 10 14  
4 3 8 5 8  
;
```

```
PROC PRINT DATA=PAIN;  
RUN;
```

Obs	SUBJ	DRUG	PAIN
1	1	1	5
2	1	2	9
3	1	3	6
4	1	4	11
5	2	1	7
6	2	2	12
7	2	3	8
8	2	4	9
9	3	1	11
10	3	2	12
11	3	3	10
12	3	4	14
13	4	1	3
14	4	2	8
15	4	3	5
16	4	4	8

Now do 2-way ANOVA with 1 obs/cell (i.e. no interaction).

$$y_{ij} = \mu + a_i + b_j + \text{epsilon}_{ij}$$

```
PROC ANOVA DATA=PAIN;
CLASS SUBJ DRUG;
MODEL PAIN=SUBJ DRUG;
MEANS DRUG/SNK;
RUN;
```

The ANOVA Procedure

Class Level Information

Class	Levels	Values
SUBJ	4	1 2 3 4
DRUG	4	1 2 3 4
Number of Observations Read		16
Number of Observations Used		16

Dependent Variable: PAIN

Source	DF	Sum of Squares	Mean Square	F Value
Model	6	120.500000	20.0833333	13.64
Error	9	13.250000	1.4722222	
Corrected Total	15	133.750000		

Source	Pr > F
Model	0.0005
Error	
Corrected Total	

R-Square	Coeff Var	Root MSE	PAIN Mean
0.900935	14.06785	1.213352	8.625000

Source	DF	Anova SS	Mean Square	F Value
SUBJ	3	70.25000000	23.41666667	15.91
DRUG	3	50.25000000	16.75000000	11.38

Source	Pr > F
SUBJ	0.0006
DRUG	0.0020

Therefore DRUG effects are not all zero: The 4 DRUGS not equally effective in treating pain.

NOTE: Denominator df=9 comes from ERROR df in the first table.

Student-Newman-Keuls Test for PAIN

NOTE: This test controls the Type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha	0.05
Error Degrees of Freedom	9
Error Mean Square	1.472222

Number of Means	2	3	4
Critical Range	1.9407923	2.3954582	2.6784122

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	DRUG
A	10.5000	4	4
A			
A	10.2500	4	2
B	7.2500	4	3
B			
B	6.5000	4	1

We see that DRUGS 4,2 and 3,1 are "same". Assuming a higher mean indicates greater pain, DRUGS 1,3 more effective in treating pain.

Now: Suppose the data were the results of assigning the 4 drugs at random to 16 subjects, then 1-Way ANOVA gives:

```
PROC ANOVA DATA=PAIN;
CLASS SUBJ DRUG;
MODEL PAIN=DRUG;
MEANS DRUG/SNK;
RUN;
```

The ANOVA Procedure

Class Level Information

Class	Levels	Values
SUBJ	4	1 2 3 4
DRUG	4	1 2 3 4

Number of Observations Read	16
Number of Observations Used	16

Dependent Variable: PAIN

Source	DF	Sum of Squares	Mean Square	F Value
Model	3	50.2500000	16.7500000	2.41
Error	12	83.5000000	6.9583333	
Corrected Total	15	133.7500000		

Source	Pr > F
Model	0.1180
Error	
Corrected Total	

R-Square	Coeff Var	Root MSE	PAIN Mean
0.375701	30.58395	2.637865	8.625000

Source	DF	Anova SS	Mean Square	F Value
DRUG	3	50.25000000	16.75000000	2.41

Source	Pr > F
DRUG	0.1180

Student-Newman-Keuls Test for PAIN

NOTE: This test controls the Type I experimentwise error rate under the complete null hypothesis but not under partial null hypotheses.

Alpha	0.05
Error Degrees of Freedom	12
Error Mean Square	6.958333

Number of Means	2	3	4
Critical Range	4.0640501	4.9760399	5.5375686

Means with the same letter are not significantly different.

SNK Grouping	Mean	N	DRUG
A	10.500	4	4
A			
A	10.250	4	2
A			
A	7.250	4	3
A			
A	6.500	4	1

We see: Before with only 4 subjects, the ERROR SS was only 13.25 with $df=9$, and the drugs effects were significant. But now with 16 subjects, the ERROR SS absorbed the SUBJ SS 70.25 and is equal to $13.25 + 70.25 = 83.5$ with $df=12$, and the drug effects are not significant.

We see: Controlling for between-subject variability reduces the error SS, and allows us to identify small treatment differences with relatively fewer subjects.

Now: use REPEATED option

Data must have the form: SUBJ PAIN1 PAIN2 PAIN3 PAIN4,
where PAIN1-PAIN4 are the dependent obs from each drug.
Notice: No DRUG factor.

```
DATA REPEAT1;  
INPUT SUBJ PAIN1-PAIN4;  
DATALINES;  
1 5 9 6 11  
2 7 12 8 9  
3 11 12 10 14  
4 3 8 5 8  
;  
  
PROC PRINT DATA=REPEAT1;  
ID SUBJ;  
RUN;
```

SUBJ	PAIN1	PAIN2	PAIN3	PAIN4
1	5	9	6	11
2	7	12	8	9
3	11	12	10	14
4	3	8	5	8

```

PROC ANOVA DATA=REPEAT1;
MODEL PAIN1-PAIN4 = /NOUNI;<--No univariate analysis for each pain variable.
REPEATED DRUG 4 (1 2 3 4);<--DRUG has 4 levels, labeled 1,2,3,4
RUN;

```

The SAS System

The ANOVA Procedure

```

Number of Observations Read      4
Number of Observations Used      4

```

Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	PAIN1	PAIN2	PAIN3	PAIN4
Level of DRUG	1	2	3	4

MANOVA Test Criteria and Exact F Statistics
for the Hypothesis of no DRUG Effect

H = Anova SSCP Matrix for DRUG

E = Error SSCP Matrix

S=1 M=0.5 N=-0.5

Statistic	Value	F Value	Num DF	Den DF	Pr > F
Wilks' Lambda	0.00909295	36.33	3	1	0.1212
Pillai's Trace	0.99090705	36.33	3	1	0.1212
Hotelling-Lawley Trace	108.97530864	36.33	3	1	0.1212
Roy's Greatest Root	108.97530864	36.33	3	1	0.1212

The ANOVA Procedure
 Repeated Measures Analysis of Variance
 Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Anova SS	Mean Square	F Value
DRUG	3	50.25000000	16.75000000	11.38
Error(DRUG)	9	13.25000000	1.47222222	

Source	Pr > F	Adj Pr > F	
		G - G	H - F
DRUG	0.0020	0.0123	0.0020
Error(DRUG)			

Greenhouse-Geisser Epsilon 0.5998 <--GG-epsilon
 Huynh-Feldt Epsilon 1.4433 <--HF-epsilon

Note:

The F test for DRUG is identical to the one from 2-Way ANOVA.

The adjusted p-valued G-G (Greenhouse-Geisser correction) and H-F (Huynh-Feldt correction) take into account correlation among the repeated measures and resort to the so called "sphericity assumption" where numerator and denominator degrees of freedom are multiplied by "epsilon", and the significance of the F ratio is evaluated with the new degrees of freedoms. Greenhouse-Geisser correction is more Conservative.

With REPEATED statement, to get pairwise comparisons use: CONTRAST(n).

In our case

DRUG CONTRAST(1) gives comparisons of 1 vs 2,3,4

DRUG CONTRAST(2) gives comparisons of 2 vs 1,3,4

DRUG CONTRAST(3) gives comparisons of 1 vs 2,3,4

This is equivalent to multiple t-tests.

For example:

```
PROC ANOVA DATA=REPEAT1;
MODEL PAIN1-PAIN4 = /NOUNI;
REPEATED DRUG 4 CONTRAST(1)/NOM SUMMARY; <--No Multivariate stats.
RUN;                                     SUMMARY requests ANOVA
```

The ANOVA Procedure

```
Number of Observations Read      4
Number of Observations Used      4
```

The ANOVA Procedure

Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	PAIN1	PAIN2	PAIN3	PAIN4
Level of DRUG	1	2	3	4

The ANOVA Procedure

Repeated Measures Analysis of Variance

Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Anova SS	Mean Square	F Value
DRUG	3	50.25000000	16.75000000	11.38
Error(DRUG)	9	13.25000000	1.47222222	

Source	Pr > F	Adj Pr > F	
		G - G	H - F
DRUG	0.0020	0.0123	0.0020
Error(DRUG)			

```
Greenhouse-Geisser Epsilon    0.5998
Huynh-Feldt Epsilon          1.4433
```

The ANOVA Procedure
 Repeated Measures Analysis of Variance
 Analysis of Variance of Contrast Variables

DRUG_N represents the contrast between the nth level of DRUG and the 1st

Contrast Variable: DRUG_2

Source	DF	Anova SS	Mean Square	F Value
Mean	1	56.25000000	56.25000000	15.70
Error	3	10.75000000	3.58333333	

Source	Pr > F
Mean	0.0287 <-- 1 and 2 not "same"
Error	

NOTE: Apparently SAS is doing matched pair comparison with $df=n-1=4-1=3$ which makes sense if "wash-out" period is perceived too short.

Contrast Variable: DRUG_3

Source	DF	Anova SS	Mean Square	F Value
Mean	1	2.25000000	2.25000000	1.42
Error	3	4.75000000	1.58333333	

Source	Pr > F
Mean	0.3189 <--1 and 3 are "same"
Error	

The ANOVA Procedure
 Repeated Measures Analysis of Variance
 Analysis of Variance of Contrast Variables

DRUG_N represents the contrast between the nth level of DRUG and the 1st

Contrast Variable: DRUG_4

Source	DF	Anova SS	Mean Square	F Value
Mean	1	64.00000000	64.00000000	19.20
Error	3	10.00000000	3.33333333	

Source	Pr > F
Mean	0.0220 <--1 and 4 are not "same"
Error	

Now PROC MIXED

The previous analysis assumes the interest focuses on the 4 subjects only. But if we think of the subjects as being a sample from a large population of subjects, then we deal with subject random effects. Many would say this is the best way to analyze our data. We can judge this by AIC, BIC!!!

```
DATA PAIN;
INPUT SUBJ @;
DO DRUG=1 TO 4;
INPUT PAIN @;
OUTPUT;
END;
DATALINES;
1 5 9 6 11
2 7 12 8 9
3 11 12 10 14
4 3 8 5 8
;
```

```

PROC MIXED DATA=PAIN;
CLASS SUBJ DRUG;
MODEL PAIN=DRUG;
RANDOM SUBJ; <---Random component. Random effects.
RUN;
QUIT;

```

The SAS System

The Mixed Procedure

Model Information

Data Set	WORK.PAIN
Dependent Variable	PAIN
Covariance Structure	Variance Components
Estimation Method	REML <-----@@@@@ The default method.
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
SUBJ	4	1 2 3 4
DRUG	4	1 2 3 4

Dimensions

Covariance Parameters	2
Columns in X	5
Columns in Z	4
Subjects	1
Max Obs Per Subject	16

Number of Observations

Number of Observations Read	16
Number of Observations Used	16
Number of Observations Not Used	0

The Mixed Procedure

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	62.87898203	
1	1	52.54100308	0.00000000

Convergence criteria met.

Covariance Parameter
Estimates

Cov Parm	Estimate	
SUBJ	5.4861	<--Subject variance.
Residual	1.4722	<--Resid variance.

Fit Statistics

-2 Res Log Likelihood	52.5
AIC (smaller is better)	56.5
AICC (smaller is better)	57.9
BIC (smaller is better)	55.3

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
DRUG	3	9	11.38	0.0020 <--Same as brfore

If we use fixed effects as in two-way ANOVA as before we get better AIC and BIC(!!!) as we see next.

```
PROC MIXED DATA=PAIN;
  CLASS SUBJ DRUG;
  MODEL PAIN=SUBJ DRUG;  <--No RANDOM component!!!
  RUN;
  QUIT;
```

The Mixed Procedure

Model Information

Data Set	WORK.PAIN
Dependent Variable	PAIN
Covariance Structure	Diagonal
Estimation Method	REML <-----@@@@@
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Residual

Class Level Information

Class	Levels	Values
SUBJ	4	1 2 3 4
DRUG	4	1 2 3 4

Dimensions

Covariance Parameters	1
Columns in X	9
Columns in Z	0
Subjects	1
Max Obs Per Subject	16

Covariance Parameter
Estimates

Cov Parm	Estimate
Residual	1.4722

Fit Statistics

-2 Res Log Likelihood	37.3
AIC (smaller is better)	39.3 <--Smaller
AICC (smaller is better)	39.9
BIC (smaller is better)	39.5 <--Smaller

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
SUBJ	3	9	15.91	0.0006
DRUG	3	9	11.38	0.0020

NOTE: This ANOVA is identical to 2-Way above.

=====

Now compare with NON-RESTRICTED ML:

Recall the mixed effects model from above:

$$y_{\{ij\}} = \mu + a_i + \beta_j + \epsilon_{\{ij\}}, \quad i, j = 1, 2, 3, 4$$

```
OPTION PS=35 LS=70;
```

```
DATA PAIN;
INPUT SUBJ @;
DO DRUG=1 TO 4;
INPUT PAIN @;
OUTPUT;
END;
DATALINES;
1 5 9 6 11
2 7 12 8 9
3 11 12 10 14
4 3 8 5 8
;
```

```
PROC MIXED DATA=PAIN METHOD=ML; <--Default is REML.
CLASS SUBJ DRUG;
MODEL PAIN=DRUG;
RANDOM SUBJ;
RUN;
QUIT;
```

The SAS System
The Mixed Procedure

Model Information

Data Set	WORK.PAIN
Dependent Variable	PAIN
Covariance Structure	Variance Components
Estimation Method	ML (Before it was REML)
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based

Degrees of Freedom Method Containment

Class Level Information

Class	Levels	Values
SUBJ	4	1 2 3 4
DRUG	4	1 2 3 4

Dimensions

Covariance Parameters	2
Columns in X	5
Columns in Z	4
Subjects	1
Max Obs Per Subject	16

The Mixed Procedure
Number of Observations

Number of Observations Read	16
Number of Observations Used	16
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Log Like	Criterion
0	1	71.84215962	
1	1	58.05818768	0.00000000

Convergence criteria met.

Covariance Parameter
Estimates

Cov Parm	Estimate
SUBJ	4.1146 (With REML get 5.4861)
Residual	1.1042 (With REML get 1.4722)

Fit Statistics

-2 Log Likelihood	58.1 (With REML get 52.5)
AIC (smaller is better)	70.1 (With REML get 56.5)
AICC (smaller is better)	79.4
BIC (smaller is better)	66.4

Type 3 Tests of Fixed Effects

Effect	DF	Num DF	Den F Value	Pr > F
DRUG	3	9	15.17	0.0007 (With REML get 0.002)

=====

Ex2. Two-Factor Repeated Experiment:
 Repeated measure on one factor.

Subjects are randomly assigned to control or treatment group. Then each subject is measured before (PRE) and after (POST) treatment. The treatment for the control group is a placebo or no treatment at all.

GROUP	SUBJ	PRE	POST
	1	80	83
Control	2	85	86
	3	83	88
	4	82	94
Treatment	5	87	93

NOTE: Subject nested within group!

6 84 98

Method I: Two-Sample t-test applied to the difference scores
 of POST-PRE to compare the difference means of the
 two groups. NOTE: Data assumed normal with equal variance.

For Control : D1=3, D2=1, D3=5
For Treatment: D1=12, D2=6, D3=14

H_0: $\mu_C = \mu_T$, H_1: μ_C not equal μ_T

```
DATA PREPOST;
INPUT SUBJ  GROUP $  PRE POST;
DIFF = POST-PRE;
DATALINES;
1 C 80 83
2 C 85 86
3 C 83 88
4 T 82 94
5 T 87 93
6 T 84 98
;
```

```
PROC TTEST DATA=PREPOST;
CLASS GROUP;
VAR DIFF;
RUN;
```

The SAS System

The TTEST Procedure

Statistics

Variable	GROUP	N	Lower CL	Mean	Upper CL	Lower CL
			Mean		Mean	Std Dev
DIFF	C	3	-1.968	3	7.9683	1.0413
DIFF	T	3	0.3244	10.667	21.009	2.1677
DIFF	Diff (1-2)		-15.07	-7.667	-0.263	1.9568

Statistics

Variable	GROUP	Std Dev	Upper CL	Std Err	Minimum	Maximum
			Std Dev			
DIFF	C	2	12.569	1.1547	1	5
DIFF	T	4.1633	26.165	2.4037	6	14
DIFF	Diff (1-2)	3.266	9.385	2.6667		

T-Tests

Variable	Method	Variances	DF	t Value	Pr > t
DIFF	Pooled	Equal	4	-2.88	0.0452 <--
DIFF	Satterthwaite	Unequal	2.88	-2.88	0.0671

Equality of Variances

Variable	Method	Num DF	Den DF	F Value	Pr > F
DIFF	Folded F	2	2	4.33	0.3750

Check:

$\text{Bar}(\text{Diff}_C) - \text{Bar}(\text{Diff}_T) = 3 - 10.667 = -7.667$

$\text{StdError}(\text{Bar}(\text{Diff}_C) - \text{Bar}(\text{Diff}_T)) = 2.6667$ with 4 df

$> -7.667 / 2.6667$

[1] -2.875089 approx -2.88 OK.

```
> pt(-2.87508,4)*2
[1] 0.04523655 approx 0.0452 OK.
```

Thus, at $\alpha=0.05$, the treatment mean difference is significantly different from the control mean difference.

Method II: Two-way ANOVA with factors GROUP and TIME, with TIME as a repeated measure.

```
DATA PREPOST;
INPUT SUBJ  GROUP $ PRE POST;
DIFF = POST-PRE;
DATALNES;
1 C 80 83
2 C 85 86
3 C 83 88
4 T 82 94
5 T 87 93
6 T 84 98
;

PROC ANOVA DATA=PREPOST;
CLASS GROUP;
MODEL PRE POST = GROUP/NOUNI;
REPEATD TIME 2 (0 1);
MEANS GROUP;
RUN;
```

The ANOVA Procedure

Class Level Information

Class	Levels	Values
GROUP	2	C T

Number of Observations Read	6
Number of Observations Used	6

Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	PRE	POST
Level of TIME	0	1

MANOVA Test Criteria and Exact F Statistics
for the Hypothesis of no TIME Effect

H = Anova SSCP Matrix for TIME

E = Error SSCP Matrix

S=1 M=-0.5 N=1

Statistic	Value	F Value	Num DF	Den DF	Pr > F
Wilks' Lambda	0.13216314	26.27	1	4	0.0069
Pillai's Trace	0.86783686	26.27	1	4	0.0069
Hotelling-Lawley Trace	6.56640625	26.27	1	4	0.0069
Roy's Greatest Root	6.56640625	26.27	1	4	0.0069

The ANOVA Procedure

Repeated Measures Analysis of Variance

MANOVA Test Criteria and Exact F Statistics
for the Hypothesis of no TIME*GROUP Effect

H = Anova SSCP Matrix for TIME*GROUP

E = Error SSCP Matrix

S=1 M=-0.5 N=1

Statistic	Value	F Value	Num DF	Den DF	Pr > F
Wilks' Lambda	0.32611465	8.27	1	4	0.0452
Pillai's Trace	0.67388535	8.27	1	4	0.0452

Hotelling-Lawley Trace	2.06640625	8.27	1	4	0.0452
Roy's Greatest Root	2.06640625	8.27	1	4	0.0452

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

Source	DF	Anova SS	Mean Square	F Value
GROUP	1	90.75000000	90.75000000	11.84
Error	4	30.66666667	7.66666667	

Source	Pr > F
GROUP	0.0263 <---Groups are different.
Error	

The ANOVA Procedure
 Repeated Measures Analysis of Variance
 Univariate Tests of Hypotheses for Within Subject Effects

Source	DF	Anova SS	Mean Square	F Value
TIME	1	140.0833333	140.0833333	26.27
TIME*GROUP	1	44.0833333	44.0833333	8.27
Error(TIME)	4	21.3333333	5.3333333	

Source	Pr > F
TIME	0.0069
TIME*GROUP	0.0452<--Interaction significant
Error(TIME)	

The ANOVA Procedure

Level of		-----PRE-----		-----POST-----	
GROUP	N	Mean	Std Dev	Mean	Std Dev
C	3	82.6666667	2.51661148	85.6666667	2.51661148

T 3 84.3333333 2.51661148 95.0000000 2.64575131

Interesting to compare with simple TWO-WAY ANOVA with GROUP at 2 levels and TIME at 2 levels as factors, and 3 obs/cell.

```
DATA PREPOST;
INPUT GROUP $ TIME $ Y @@;
DATALINES;
C PRE 80 C POST 83
C PRE 85 C POST 86
C PRE 83 C POST 88
T PRE 82 T POST 94
T PRE 87 T POST 93
T PRE 84 T POST 98
;

PROC ANOVA DATA=PREPOST;
CLASS GROUP TIME;
MODEL Y = GROUP TIME GROUP*TIME;
RUN;
```

The ANOVA Procedure

Class Level Information

Class	Levels	Values
GROUP	2	C T
TIME	2	POST PRE

Number of Observations Read	12
Number of Observations Used	12

Dependent Variable: Y

Source	DF	Sum of Squares	Mean Square	F Value
--------	----	----------------	-------------	---------

Model	1+1+1=3	274.9166667	91.6388889	14.10
Error	2*2*(3-1)=8	52.0000000	6.5000000	
Corrected Total	12-1=11	326.9166667		

Source	Pr > F
Model	0.0015
Error	
Corrected Total	

R-Square	Coeff Var	Root MSE	Y Mean
0.840938	2.933281	2.549510	86.91667

Source	DF	Anova SS	Mean Square	F Value
GROUP	1	90.7500000	90.7500000	13.96
TIME	1	140.0833333	140.0833333	21.55

Source	Pr > F
GROUP	0.0057 <--Sig
TIME	0.0017 <--Sig

Dependent Variable: Y

Source	DF	Anova SS	Mean Square	F Value
GROUP*TIME	(2-1)(2-1)=1	44.0833333	44.0833333	6.78

Source	Pr > F
GROUP*TIME	0.0314 <--Sig