

# Repeated Measures Analysis

Design of Experiments - Montgomery  
Section 14-4

## Repeated Measures

- Often take measurements on EU over time
- 1 Single summary of time points
  - Peak response or total concentration in body
  - Response mean or orth polynomials (shape summary)
  - Typically RCBD or CRD on summary statistic
- 2 Interested in time as a factor
  - Interaction of trts with time
  - Shape of response curve over time
- Common to take Split Plot approach
  - Subject is whole plot
  - Time units are subplot
- Problems
  - Assumptions: With large changes in response over time, may have problems with constant variance assumption
  - Non-randomness of time: Not randomly applying time to subplot EU. Observations at adjacent times more correlated than times further away.
- Other approaches (when time a factor)
  - Multivariate analysis (takes correlation into account)
  - Proc Mixed to model correlation structure

## Example

- Consider pretest/posttest problem
- Subject assigned to trt group
- Measurements taken pre and 2 post treatment
- Use pre-test score to standardize post

Subject	Trt	Pretest	Post1	Post2	Ave Post	Diff
1	1	100	125	135	130.0	30.0
2	2	110	125	125	125.0	15.0
3	2	90	105	104	104.5	14.5
4	1	110	130	139	134.5	24.5
5	1	105	130	141	135.5	30.5
6	2	125	135	136	135.5	10.5

- Perform t-test of diffs (remove time as factor)

$$\frac{28.33 - 13.33}{\sqrt{8.583(\frac{1}{4} + \frac{1}{4})}} = 6.27$$

$$P = .0033$$

- Treat as split plot design
  - Use only post test scores (adjusted for pre-test)

Source	DF	SS	MS	F	P
TRT	1	675.00	675.00	39.32	.0033
SUBJ(TRT)	4	68.67	17.17		
TIME	1	75.00	75.00	150.00	.0003
TIME*TRT	1	75.00	75.00	150.00	.0003
ERROR	4	2.00	0.50		

## Split-Plot Approach

- Split plot compares trts by averaging over time
- If other summary of obs desired, use CRD/RCBD
- Provides info on time and time\*trt interaction
- Are these P-values correct?
- Not properly randomized (time only moves forward)
- Recall single factor CRD split-plot model

$$\text{Var}(y_{ijk}) = \sigma_R^2 + \sigma^2$$

$$\text{Cor}(y_{ijk}, y_{ij'k}) = \sigma_R^2 / (\sigma_R^2 + \sigma^2)$$

Any two obs in same whole plot has same correlation  
Known as assumption of compound symmetry

**Split plot approach appropriate when repeated measures have compound symmetry**

## Huyhn-Feldt Conditions

(JASA, 1970)

- Split-plot analysis valid under these conditions
- Less restrictive than compound symmetry
- Also known as sphericity condition
- Instead of constant correlation

$$\text{Var}(y_{ijk} - y_{ij'k}) = c$$

- In SAS, tests for sphericity assumptions
- Adjusts F for deviations from these conditions
  - H-F and G-G adjust F-values (multiply F by number 0-1)

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## Example

Studying different methods (two methods and control) to increase speed of throwing a baseball. Assume seven subjects were assigned to each group and followed a specific training method for one month. Each subject's throwing velocity (km/hr) was observed at the end of two and four weeks (adjusted for initial throwing velocity)

Repeated measures problem. Subjects nested within method. While the EU for method is the subject, we're interested in relationship over time so we want to include time in the model.

$$y_{ijkl} = \mu + M_i + S_{j(i)} + T_k + MT_{ik} + ST_{jk(i)} + \epsilon_{i(j)k}$$

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## SAS Program using GLM

```
options nocenter ls=75;

data new;
input meth subj time1 time2;
resp=time1; time=1; output;
resp=time2; time=2; output;
cards;
1 1 25.4 30.6
1 2 27.4 29.3
1 3 25.5 30.0
. . . .
3 7 25.6 24.8
;

proc glm;
class meth subj time;
model resp=meth subj(meth) time meth*time;
test h=meth e=subj(meth);
means meth|time;
```

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Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	161.45690	7.01987	5.31	0.0003
Error	18	23.80143	1.32230		
Corrected Total	41	185.25833			

Source	DF	Type III SS	Mean Square	F Value	Pr > F
METH	2	52.431905	26.215952	19.83	0.0001
SUBJ(METH)	18	38.261429	2.125635	1.61	0.1614
TIME	1	53.268810	53.268810	40.28	0.0001
METH*TIME	2	17.494762	8.747381	6.62	0.0070

Test of Hypotheses using the Type III MS for SUBJ(METH) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
METH	2	52.431905	26.215952	12.33	0.0004

Level of METH	N	Mean	SD
1	14	27.5714286	2.22552624
2	14	27.1571429	2.06647760
3	14	25.0214286	0.99705611

Level of TIME	N	Mean	SD
1	21	25.4571429	1.35593932
2	21	27.7095238	2.18194976

Level of METH	Level of TIME	N	Mean	SD
1	1	7	25.7857143	0.86106247
1	2	7	29.3571429	1.59672283
2	1	7	25.8142857	1.87299099
2	2	7	28.5000000	1.23962360
3	1	7	24.7714286	1.02747958
3	2	7	25.2714286	0.97590007

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# Using REPEATED in Proc GLM

- Repeated command does several analyses
  - Multivariate Analysis
  - Split Plot (with HF and GG df corrections)
  - Orthogonal polynomials (single df summaries)

```
options nocenter ls=75;
data new;
input meth subj time1 time2;
cards;
1 1 25.4 30.6
1 2 27.4 29.3
1 3 25.5 30.0
. . . .
3 5 24.5 26.2
3 6 25.6 26.9
3 7 25.6 24.8
;

proc glm;
class meth subj;
model time1 time2 = meth;
repeated time 2 (1 2) polynomial / summary;
```

## General Linear Models Procedure

Dependent Variable: TIME1

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	4.9400000	2.4700000	1.40	0.2730
Error	18	31.8314286	1.7684127		
Corrected Total	20	36.7714286			

Source	DF	Type III SS	Mean Square	F Value	Pr > F
METH	2	4.9400000	2.4700000	1.40	0.2730

Dependent Variable: TIME2

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	64.986667	32.493333	19.35	0.0001
Error	18	30.231429	1.679524		
Corrected Total	20	95.218095			

Source	DF	Type III SS	Mean Square	F Value	Pr > F
METH	2	64.986667	32.493333	19.35	0.0001

## Repeated Measures Analysis of Variance

Repeated Measures Level Information

Dependent Variable	TIME1	TIME2
Level of TIME	1	2

Manova Test Criteria and Exact F Statistics for the Hypothesis of no TIME Effect  
 H = Type III SS&CP Matrix for TIME E = Error SS&CP Matrix

S=1 M=-0.5 N=8

Statistic	Value	F	Num DF	Den DF	Pr > F
Wilks' Lambda	0.308827755	40.2849	1	18	0.0001
Pillai's Trace	0.691172245	40.2849	1	18	0.0001
Hotelling-Lawley Trace	2.238050937	40.2849	1	18	0.0001
Roy's Greatest Root	2.238050937	40.2849	1	18	0.0001

Manova Test Criteria and Exact F Statistics for the Hypothesis of no TIME\*METH Effect  
 H = Type III SS&CP Matrix for TIME\*METH E = Error SS&CP Matrix

S=1 M=0 N=8

Statistic	Value	F	Num DF	Den DF	Pr > F
Wilks' Lambda	0.57635894	6.61527	2	18	0.0070
Pillai's Trace	0.42364106	6.61527	2	18	0.0070
Hotelling-Lawley Trace	0.73502991	6.61527	2	18	0.0070
Roy's Greatest Root	0.73502991	6.61527	2	18	0.0070

## General Linear Models Procedure

Repeated Measures Analysis of Variance  
 Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
METH	2	52.4319	26.2160	12.33	0.0004
Error	18	38.2614	2.1256		

## Repeated Measures Analysis of Variance

Univariate Tests of Hypotheses for Within Subject Effects

Source: TIME

DF	Type III SS	Mean Square	F Value	Pr > F	Adj G - G	Pr > F H - F
1	53.26880952	53.26880952	40.28	0.0001	.	.

Source: TIME\*METH

DF	Type III SS	Mean Square	F Value	Pr > F	Adj G - G	Pr > F H - F
2	17.49476190	8.74738095	6.62	0.0070	.	.

Source: Error(TIME)

DF	Type III SS	Mean Square
18	23.80142857	1.32230159

## 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	53.2688095	53.2688095	40.28	0.0001
METH	2	17.4947619	8.7473810	6.62	0.0070
Error	18	23.8014286	1.3223016		

## Example now with 3 time pts

- Consider another test given after additional 2 weeks.  
No training.

```
options nocenter ps=50 ls=72;

data new;
input meth subj time1 time2 time3;
resp=time1; time=1;output;
resp=time2; time=2;output;
resp=time3; time=3;output;
cards;
1 1 25.4 30.6 29.1
1 2 27.4 29.3 28.0
1 3 25.5 30.0 27.0
1 4 25.8 29.7 27.9
. . . . .
3 6 25.6 26.9 29.2
3 7 25.6 24.8 28.9
;

proc glm;
class meth;
model time1 time2 time3 = meth /nouni;
repeated time (0 1 2) polynomial / summary;

proc sort; by meth;

proc means; var time1-time3;by meth;
```

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METH=1					
Variable	N	Mean	Std Dev	Minimum	Maximum
TIME1	21	25.7857143	0.8168756	24.6000000	27.4000000
TIME2	21	29.3571429	1.5147843	26.6000000	31.3000000
TIME3	21	28.0142857	0.9253571	26.6000000	29.2000000

  

METH=2					
Variable	N	Mean	Std Dev	Minimum	Maximum
TIME1	21	25.8142857	1.7768753	22.9000000	28.5000000
TIME2	21	28.5000000	1.1760102	27.1000000	29.7000000
TIME3	21	28.3571429	1.5702138	26.2000000	30.4000000

  

METH=3					
Variable	N	Mean	Std Dev	Minimum	Maximum
TIME1	21	24.7714286	0.9747527	22.8000000	25.6000000
TIME2	21	25.2714286	0.9258201	24.0000000	26.9000000
TIME3	21	28.5714286	1.4906854	26.2000000	31.0000000

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Manova Test Criteria and Exact F Statistics for  
the Hypothesis of no TIME Effect  
H = Type III SS&CP Matrix for TIME E = Error SS&CP Matrix

S=1 M=0 N=7.5

Statistic	Value	F	Num DF	Den DF	Pr > F
Wilks' Lambda	0.151187618	47.7215	2	17	0.0001
Pillai's Trace	0.848812382	47.7215	2	17	0.0001
Hotelling-Lawley Trace	5.614298261	47.7215	2	17	0.0001
Roy's Greatest Root	5.614298261	47.7215	2	17	0.0001

Manova Test Criteria and F Approximations for  
the Hypothesis of no TIME\*METH Effect  
H = Type III SS&CP Matrix for TIME\*METH E = Error SS&CP Matrix

S=2 M=-0.5 N=7.5

Statistic	Value	F	Num DF	Den DF	Pr > F
Wilks' Lambda	0.279947604	7.56499	4	34	0.0002
Pillai's Trace	0.720952246	5.07297	4	36	0.0024
Hotelling-Lawley Trace	2.568882652	10.2755	4	32	0.0001
Roy's Greatest Root	2.567630776	23.1087	2	18	0.0001

NOTE: F Statistic for Roy's Greatest Root is an upper bound.  
NOTE: F Statistic for Wilks' Lambda is exact.

Repeated Measures Analysis of Variance  
Tests of Hypotheses for Between Subjects Effects

Source	DF	Type III SS	Mean Square	F Value	Pr > F
METH	2	29.0375	14.5187	4.20	0.0319
Error	18	62.2667	3.4593		

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Source: TIME

DF	Type III SS	Mean Square	F Value	Pr > F	Adj G - G	Pr > F H - F
2	95.21555556	47.60777778	46.63	0.0001	0.0001	0.0001

Source: TIME\*METH

DF	Type III SS	Mean Square	F Value	Pr > F	Adj G - G	Pr > F H - F
4	41.99492063	10.49873016	10.28	0.0001	0.0001	0.0001

Source: Error(TIME)

DF	Type III SS	Mean Square
36	36.75619048	1.02100529

Greenhouse-Geisser Epsilon = 0.9194  
Huynh-Feldt Epsilon = 1.1328

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	85.7142857	85.7142857	100.93	0.0001
METH	2	4.8400000	2.4200000	2.85	0.0841
Error	18	15.2857143	0.8492063		

Contrast Variable: TIME.2

Source	DF	Type III SS	Mean Square	F Value	Pr > F
MEAN	1	9.5012698	9.5012698	7.97	0.0113
METH	2	37.1549206	18.5774603	15.57	0.0001
Error	18	21.4704762	1.1928042		

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## Split Plot Analysis

```
data new1;
set new;
resp=time1; time=1; output;
resp=time2; time=2; output;
resp=time3; time=3; output;

proc glm data=new1;
class meth subj time;
model resp = meth subj(meth) time meth*time;
test h=meth e= subj(meth);
means meth*time;
```

```
-----
Dependent Variable: resp

Source          DF          Sum of
                Squares    Mean Square  F Value  Pr > F
Model           26      228.5146032    8.7890232    8.61  <.0001
Error           36       36.7561905    1.0210053
Corrected Total 62      265.2707937

Source          DF      Type III SS    Mean Square  F Value  Pr > F
meth            2      29.03746032    14.51873016    14.22  <.0001
subj(meth)     18      62.26666667    3.45925926    3.39  0.0009
time            2      95.21555556    47.60777778    46.63  <.0001
meth*time       4      41.99492063    10.49873016    10.28  <.0001

Tests of Hypotheses Using the Type III MS for subj(meth) as an Error Term
Source          DF      Type III SS    Mean Square  F Value  Pr > F
meth            2      29.03746032    14.51873016    4.20  0.0319
```

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## Analysis Using Proc Mixed

- Consider covariance of obs within subject
- MIXED allows for different covariance structures
- Recall Latin Square as repeated measures problem
- Uses simple ( $\sigma^2 I$ ) as default (indep)

Assume three time points per subject

$$\sigma^2 I = \begin{bmatrix} \sigma^2 & 0 & 0 \\ 0 & \sigma^2 & 0 \\ 0 & 0 & \sigma^2 \end{bmatrix}$$

- Use one of various provided
- Create your own

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## Covariance Structures

Consider three time points per subject

- Compound Symmetry

$$\begin{bmatrix} \sigma^2 + \sigma_1^2 & \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma^2 + \sigma_1^2 & \sigma_1^2 \\ \sigma_1^2 & \sigma_1^2 & \sigma^2 + \sigma_1^2 \end{bmatrix}$$

- Unstructured

$$\begin{bmatrix} \sigma_{11}^2 & \sigma_{21} & \sigma_{31} \\ \sigma_{21} & \sigma_{22}^2 & \sigma_{32} \\ \sigma_{31} & \sigma_{32} & \sigma_{33}^2 \end{bmatrix}$$

- First order autoregressive

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

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## Example

```
options nocenter ls=75;
data new;
input meth subj time1 time2 time3;
resp=time1; time=1; person=7*(meth-1)+subj;output;
resp=time2; time=2; person=7*(meth-1)+subj;output;
resp=time3; time=3; person=7*(meth-1)+subj;output;
drop time1-time3;
cards;
1 1 26.25 29.50 31.53
1 2 24.33 27.62 28.45
.
.
3 6 28.09 28.33 29.04
3 7 27.55 27.86 29.33
;

proc mixed;
class meth subj time;
model resp=meth time*meth time;
random subj(meth);
```

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## Other Correlation Structures

```
proc mixed;
class meth subj time;
model resp = meth time meth*time;
random subj(meth);
repeated / subject=person type=un r;
```

```
proc mixed;
class meth subj time;
model resp = meth time meth*time;
random subj(meth);
repeated / subject=person type=cs r;
```

```
proc mixed;
class meth subj time;
model resp = meth time meth*time;
random subj(meth);
repeated / subject=person type=ar(1) r;
```

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### Covariance Parameter Estimates (REML)

Cov Parm	Estimate
SUBJ(METH)	0.81275132
Residual	1.02100529

### Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
METH	2	18	4.20	0.0319
TIME	2	36	46.63	0.0001
METH*TIME	4	36	10.28	0.0001

### Covariance Parameter Estimates (REML)

Cov Parm	Subject	Estimate
SUBJ(METH)		0.81275132
CS	PERSON	0.00000000
Residual		1.02100529

### Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
METH	2	18	4.20	0.0319
TIME	2	36	46.63	0.0001
METH*TIME	4	36	10.28	0.0001

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### R Matrix for Subject 1

Row	COL1	COL2	COL3
1	0.79349206	-0.57325397	0.08674603
2	-0.57325397	0.70460317	
3	0.08674603		1.07841270

### Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
METH	2	18	4.20	0.0319
TIME	2	36	50.53	0.0001
METH*TIME	4	36	11.56	0.0001

### R Matrix for Subject 1

Row	COL1	COL2	COL3
1	0.89120796	-0.23078429	0.05976314
2	-0.23078429	0.89120796	-0.23078429
3	0.05976314	-0.23078429	0.89120796

### Covariance Parameter Estimates (REML)

Cov Parm	Subject	Estimate
SUBJ(METH)		0.93410237
AR(1)	PERSON	-0.25895672
Residual		0.89120796

### Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
METH	2	18	4.24	0.0310
TIME	2	36	55.44	0.0001
METH*TIME	4	36	9.08	0.0001

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