Mixed Model Repeated Measures (MMRM)

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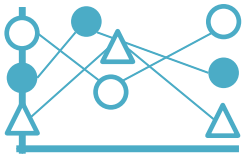
Agenda

- What is Repeated measure
- What is Repeated measure analysis
- Assumptions
- How Repeated measure ANOVA Summary looks like
- SAS Syntax – proc mixed, sas output
- Types of covariance structure, definition, SAS syntax, ouput
- SAS Syntax – proc genmod, sas output

What is Repeated Measure?

Measured at fixed time points

Serial evaluation over time on the same patient



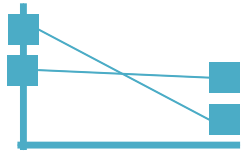
Measurements over multiple visits, known as ‘longitudinal’ data over time.

THESE MEASUREMENTS CANNOT BE CONSIDERED AS INDEPENDENT.

What is Repeated Measure Analysis?

Covariance & correlation Structure

F-Test



Treatment-by-time Interaction

Assumptions

01.

Normality and variance homogeneity (homoscedasticity)

02.

In Univariate ANOVA, each pair of repeated measures has the same correlations known as “compound symmetry”

03.

Hypothesis of equality of mean responses among treatments, ‘averaged’ over time. i.e. no treatment-by-time interaction.

ANOVA Summary for Repeated-Measures Design

Let 'n_i' represent no of patients(PAT) in 'g' independent treatment groups(TREAT) (i = 1, 2, ….. ,g) are subjected to repeated measurements of the same response at 't' equally spaced time period(VISIT).

$N=n_1+n_2+n_3+\ldots+n_g$.

SOURCE	df	SS	MS	F
TREAT	g-1	SSG	MSG	F_G=MSG/MSP(G)
PAT(within TREAT)	N-g	SSP(G)	MSP(G)	--
VISIT	t-1	SST	MST	F_T=MST/MSE
TREAT -by- VISIT	(g-1)(t-1)	SSGT	MSGT	F_{GT}=MSGT/MSE
Error	(N-g)(t-1)	SSE	MSE	--
Total	Nt-1	TOT(SS)		

ANOVA Summary for Repeated-Measures Design

VARIATION FROM PATIENT-TO-PATIENT is one type of **random error**, as estimated by the mean square MSP(G) for **Patient (within Treatment).**

TREATMENT EFFECT The mean square for Treatment (MSG) is an estimate of **among-patient variability**. The ratio of independent estimates MSG and random error variation MSP(G) (F_t = MSG /MSP(G)) used to test the hypothesis of no Treatment effect.

VISIT EFFECT The mean square for Time (MST) is an estimate of **within-patient variability**. The ratio of MST and error variation MSE estimates (F_t = MST/MSE) estimated to test the hypothesis of no Time effect.

TREATMENT-BY-VISIT INTERACTION EFFECT Interaction means square, MSGT, which is also a measure of **within-patient variation.** Under H_0, is compared to the MSE to test significant of **Treatment-by-Time interaction**.

MMRM Analysis - Proc Mixed Syntax

PROC MIXED | Specify a model that uses the most appropriate correlation patterns among pairs of measurements across time.

```
ODS SELECT MIXED.RCORR MIXED.FITSTATISTICS MIXED.TESTS3;
PROC MIXED DATA = DISCOM;
    CLASS TREAT MONTH PAT;
    MODEL SCORE = TREAT MONTH TREAT*MONTH;
    REPEATED MONTH/ TYPE=UN SUBJECT=PAT(TREAT) RCORR;
    TITLE4 'PROC MIXED USING UNSTRUCTURED COVARIANCE (UN)';
RUN;
```

THE UNSTRUCTURED APPROACH (TYPE=UN) MAKES NO ASSUMPTION ABOUT THE CORRELATIONS AMONG VISITS.

If Convergence Criteria is met

PROC MIXED USING UNSTRUCTURED COVARIANCE (UN)

The Mixed Procedure

Estimated R Correlation Matrix for PAT(TREAT) 2 H						
Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.9005	0.7703	0.8002	0.7763	0.7773
2	0.9005	1.0000	0.8179	0.7995	0.7521	0.7261
3	0.7703	0.8179	1.0000	0.8738	0.7223	0.7418
4	0.8002	0.7995	0.8738	1.0000	0.8628	0.8273
5	0.7763	0.7521	0.7223	0.8628	1.0000	0.9206
6	0.7773	0.7261	0.7418	0.8273	0.9206	1.0000

Fit Statistics	
-2 Res Log Likelihood	2649.9
AIC (Smaller is Better)	2691.9
AICC (Smaller is Better)	2694.1
BIC (Smaller is Better)	2741.9

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TREAT	2	77	0.94	0.3967
MONTH	5	77	21.55	<.0001
TREAT*MONTH	10	77	2.08	0.0357

Interpretation

01. At significance level α=0.05 ,output shows Treatment-by-Month interaction is significant with p value 0.0357 using the unstructured covariance.

02. Fit Statistics provides an indication of relative goodness of fit, smaller AIC values suggesting a better fit.

Proc Mixed | Covariance Structures

You can specify following covariance structures by using the same MODEL statement in PROC MIXED .

1. First order autoregressive (AR(1)) ,
2. Auto-Regressive Moving Average Covariance(ARMA(1,1))
3. Toeplitz(TOEP) ,and
4. Compound symmetric (CS)

THE COVARIANCE STRUCTURE SPECIFIED IN PROC MIXED WILL MODEL THE VARIANCE ASSUMPTIONS AT DIFFERENT TIME POINTS AND THE PATTERNS OF CORRELATIONS

Proc Mixed | Covariance Structures

In the first-order autoregressive structure **(TYPE =AR(1)),** measurements taken at adjacent time points (e.g. consecutive visits) have the same correlation such as ρ.

The correlation of ρ2 is assigned to measurements that are 2 visits apart;

ρ3, to measurements that are 3 visits apart, etc.

$$\sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

```
REPEATED/TYPE=AR(1) SUBJECT=PAT(TREAT);
```

PROC MIXED USING First-Order Auto-Regressive COVARIANCE (AR(1))

Estimated R Correlation Matrix for PAT(TREAT) 2 H						
Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.8801	0.7746	0.6817	0.6000	0.5281
2	0.8801	1.0000	0.8801	0.7746	0.6817	0.6000
3	0.7746	0.8801	1.0000	0.8801	0.7746	0.6817
4	0.6817	0.7746	0.8801	1.0000	0.8801	0.7746
5	0.6000	0.6817	0.7746	0.8801	1.0000	0.8801
6	0.5281	0.6000	0.6817	0.7746	0.8801	1.0000

Fit Statistics	
-2 Res Log Likelihood	2698.2
AIC (Smaller is Better)	2702.2
AICC (Smaller is Better)	2702.2
BIC (Smaller is Better)	2706.9

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TREAT	2	77	0.94	0.3952
MONTH	5	359	11.21	<.0001
TREAT*MONTH	10	359	1.43	0.1671

Proc Mixed | Covariance Structures

The autoregressive moving average (**TYPE =ARMA(1,1)**) is similar, except the entries that involve powers of ρ are multiplied by a constant, λ(0 < λ < 1).

$$\lambda\,\sigma^2\begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

```
REPEATED / TYPE=ARMA(1,1)
SUBJECT=PAT(TREAT);
```

PROC MIXED USING First-Order Auto-Regressive Moving Average Covariance ARMA(1,1)

Estimated R Correlation Matrix for PAT(TREAT) 2 H						
Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.8772	0.8134	0.7543	0.6994	0.6486
2	0.8772	1.0000	0.8772	0.8134	0.7543	0.6994
3	0.8134	0.8772	1.0000	0.8772	0.8134	0.7543
4	0.7543	0.8134	0.8772	1.0000	0.8772	0.8134
5	0.6994	0.7543	0.8134	0.8772	1.0000	0.8772
6	0.6486	0.6994	0.7543	0.8134	0.8772	1.0000

Fit Statistics	
-2 Res Log Likelihood	2691.2
AIC (Smaller is Better)	2697.2
AICC (Smaller is Better)	2697.2
BIC (Smaller is Better)	2704.3

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TREAT	2	77	0.90	0.4116
MONTH	5	359	14.02	<.0001
TREAT*MONTH	10	359	1.47	0.1478

Proc Mixed | Covariance Structures

The Toeplitz structure (**TYPE=TOEP**) is more general. It assigns a correlation of
ρ_1 to measurements taken from consecutive visits; a correlation
ρ_2 for two measurements that are taken 2 visits apart;
ρ_3 to two measurements that are taken 3 visits apart, etc.

$$\begin{bmatrix} \sigma^2 & \sigma_1 & \sigma_2 & \sigma_3 \\ \sigma_1 & \sigma^2 & \sigma_1 & \sigma_2 \\ \sigma_2 & \sigma_1 & \sigma^2 & \sigma_1 \\ \sigma_3 & \sigma_2 & \sigma_1 & \sigma^2 \end{bmatrix}$$

```
REPEATED / TYPE=TOEP SUBJECT=PAT(TREAT);
```

PROC MIXED USING Toeplitz COVARIANCE (TOEP)

Estimated R Correlation Matrix for PAT(TREAT) 2 H

Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.8776	0.7931	0.7741	0.7475	0.7708
2	0.8776	1.0000	0.8776	0.7931	0.7741	0.7475
3	0.7931	0.8776	1.0000	0.8776	0.7931	0.7741
4	0.7741	0.7931	0.8776	1.0000	0.8776	0.7931
5	0.7475	0.7741	0.7931	0.8776	1.0000	0.8776
6	0.7708	0.7475	0.7741	0.7931	0.8776	1.0000

Fit Statistics	
-2 Res Log Likelihood	2671.1
AIC (Smaller is Better)	2683.1
AICC (Smaller is Better)	2683.3
BIC (Smaller is Better)	2697.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
TREAT	2	77	0.91	0.4077
MONTH	5	359	19.65	<.0001
TREAT*MONTH	10	359	2.06	0.0266

Proc Mixed | Covariance Structures

As seen previously, the compound symmetric structure (**TYPE=CS**) assumes the same the correlation, is constant regardless of how far apart the measurements are.

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

```
REPEATED / TYPE=CS SUBJECT=PAT(TREAT);
```

PROC MIXED USING Compound Symmetric Covariance (CS)

Estimated R Correlation Matrix for PAT(TREAT) 2 H						
Row	Col1	Col2	Col3	Col4	Col5	Col6
1	1.0000	0.8038	0.8038	0.8038	0.8038	0.8038
2	0.8038	1.0000	0.8038	0.8038	0.8038	0.8038
3	0.8038	0.8038	1.0000	0.8038	0.8038	0.8038
4	0.8038	0.8038	0.8038	1.0000	0.8038	0.8038
5	0.8038	0.8038	0.8038	0.8038	1.0000	0.8038
6	0.8038	0.8038	0.8038	0.8038	0.8038	1.0000

Fit Statistics	
-2 Res Log Likelihood	2743.5
AIC (Smaller is Better)	2747.5
AICC (Smaller is Better)	2747.5
BIC (Smaller is Better)	2752.2

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
TREAT	2	77	0.88	0.4172
MONTH	5	359	26.69	<.0001
TREAT*MONTH	10	359	2.30	0.0125

GEE Analysis | PROC GENMOD

01.

Generalized estimating equations (GEE)

02.

GEE modelling methodology also produce good estimates

03.

GEE analysis requires **correlation structure**

- *Compound symmetric (**CS**)*
- *Unstructured (**UN**)*
- *User defined correlation structure*

04.

Provides results for checking **TREAT -by-VISIT interaction**

SAS Syntax for PROC GENMOD

```
ODS SELECT
    Genmod.Type3; TITLE4 'GEE Analysis Using PROC GENMOD';
 PROC GENMOD DATA = UNIALZ;
  CLASS TREAT MONTH PAT;
  MODEL ADASCOG = TREAT MONTH TREAT*MONTH / DIST = NORMAL
  TYPE3;
  REPEATED MONTH SUBJECT = PAT / TYPE = AR(1);
  TITLE5 'Autoregressive Correlation (AR(1)) Working Correlation';
RUN;
```

Output

GEE Analysis Using PROC GENMOD
Autoregressive Correlation (AR(1)) Working Correlation

Score Statistics For Type 3 GEE Analysis			
Source	DF	Chi-Square	Pr > ChiSq
TREAT	2	2.02	0.3639
MONTH	5	46.14	<.0001
TREAT*MONTH	10	21.76	0.0164

SAS Code for Example 1 (PROC GENMOD)

```
REPEATED SUBJECT =PAT / TYPE =CS;
```

Output

GEE Analysis Using PROC GENMOD
compound symmetric (CS) Correlation structure

Score Statistics For Type 3 GEE Analysis			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
TREAT	2	1.96	0.3745
MONTH	5	45.41	<.0001
TREAT*MONTH	10	21.28	0.0192

```
REPEATED SUBJECT =PAT /
TYPE=USER(1.0  0.9  0.8  0.7  0.7  0.7
          0.9  1.0  0.9  0.8  0.7  0.7
          0.8  0.9  1.0  0.9  0.8  0.7
          0.7  0.8  0.9  1.0  0.9  0.8
          0.7  0.7  0.8  0.9  1.0  0.9
          0.7  0.7  0.7  0.8  0.9  1.0);
```

Output

GEE Analysis Using PROC GENMOD
user-defined Correlation structure (USER())

Score Statistics For Type 3 GEE Analysis			
Source	**DF**	**Chi-Square**	**Pr > ChiSq**
TREAT	2	2.05	0.3582
MONTH	5	45.39	<.0001
TREAT*MONTH	10	21.44	0.0182

References

1. *SAS Institute Inc. 2011. SAS/STAT® 9.2 User's Guide*. Cary, NC: SAS Institute Inc.
2. *"Common Statistical Methods for Clinical Research with SAS Examples, Second Edition"*- Glenn A. Walker

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Your comments and questions are valued and encouraged.

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Thank you.

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