# Repeated Measures Analysis

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# Agenda

1. Introduction to Repeated Measures
2. Building models:
3. PROC MIXED
4. Syntax
5. REPEATED statement
6. Covariance Structures
7. Examples and QA

# Repeated Measures: Introduction & Basics

+ Refers to data set with multiple measurement (made over a period of time) of response variable on the same experimental unit.
+ Data consists of multiple measurements on experimental units such as individuals, animals or machines.
+ Experimental Design: <u>Completely randomized Design</u>
+ Factors:
  + **Treatment** (Between subjects)
  + **Time** (Within subjects)

# Why Repeated measures?

- Experimental design has goal of reducing error and minimizing bias: E.g, Using Randomized blocks.
- Individuals are ‘**Blocks**’ in repeated measures.
- Can conduct complex designs with fewer experimental units
- Involves covariance structure: Particularly the error variance covariance structure
- Adjacent observations are likely to be more **correlated** than more distant observations

# Objectives

+ Important feature of repeated measure experiments: Correlation pattern among the responses on the same individual over time.
+ To test difference between treatment means and changes in treatment means over time.
+ To test covariance structure of the observed data.
+ In repeated measures ANOVA, the effects of interest are:
  + Between-subject effects such as TREATMENT
  + Within-Subject effects such as TIME
  + Interaction between two effects: TREATMENT *TIME

# Some examples / applications

+ ECG (QTc) monitoring following drug administration
+ Weight of subjects at daily/weekly intervals
+ FEV1 measurements following inhalation of therapeutic substance
+ Laboratory parameter measurements at certain time-points
+ Cross-over Studies
+ Long term monitoring studies

# Repeated Measures Designs

- Univariate and Multivariate Approaches
  - Univariate
    - Randomized Designs
    - Split-plot designs
  - Multivariate:
    - MANOVA
  - Mixed Model Analysis
    - GLMM (**G**eneral **L**inear **M**ixed **M**odel)
- **Mixed Model** Approach is preferred method

# Building the analysis model

1. Model the mean structure, by specifying the fixed effects.
2. Specify the covariance structure: Between subjects and Within subjects.
3. Fit the mean model accounting for the covariance structure.
4. Make statistical inference based on the results of step 4.

## MIXED model

*Statistical Notations*:

- Let $\mathbf{Y}_{ij}$ = outcome for $\mathbf{i}^{th}$ person, $\mathbf{j}^{th}$ measurement
- Let Y be a vector of all outcomes for all subjects
- X is a matrix of independent variables
- Z is a matrix associated with random effects

# MIXED model formulation (Contd)

## Model: $Y = X_{\beta} + Z_{\gamma} + \varepsilon$

**β** are the **fixed effect** parameters

- Similar to the coefficients in a regression model
- Coefficients tell us how variables are associated with the outcome
- Some coefficients (of time and interactions with time) will also tell us how variables are associated with change in the outcome

**γ** is the unknown vector of **random effects**, $\gamma \sim N(0, \Sigma)$

**ε** are the errors, i.e, residual effect being the difference between the modelled value and the observed value for each subject

**ε** $\sim N(0, R)$. (Ex: $R=\sigma^2$)

Variance-Covariance Matrix of the model **$V = ZGZ' + R$**

# Repeated Measures MIXED Model

- Simplified structure of the model:

$$y_{ijk} = \mu + \alpha_i + \gamma_k + (\alpha\gamma)_{ik} + u_{ij} + e_{ijk}$$

Where,

- $Y_{ijk}$ is response at time $k$ for the $j^{th}$ subject in the $i^{th}$ group
- $\mu$, $\alpha_i$, $\gamma_k$, and $(\alpha\gamma)_{ik}$ are fixed effects
- $u_{ij}$ is the random effect corresponding to the $j^{th}$ subject in the $i^{th}$ group
- $e_{ijk}$ is random error

# MIXED model formulation (Contd)

+ Assumptions of Model
  - Linearity
  - Homoscedasticity (constant variance)
  - Errors are normally distributed
  - Random effects are normally distributed
  - Typically assume Missing At Random (MAR)

+ Graphical tools for checking assumptions
  - Scatter Plot
  - Quantile-Quantile plot (QQ plot)

+ Mixed Model uses 3 approaches to variance component estimation
  1. ANOVA
  2. Maximum likelihood (ML)
  3. **Re**stricted **m**aximum **l**ikelihood (**REML**)

# General Linear Model vs Linear Mixed Model

## General Linear Model

The parameters in a GLM are $\beta$ and $\sigma^2$

$$\boldsymbol{Y}_i = \underbrace{\boldsymbol{X}_i\boldsymbol{\beta}}_{\text{fixed}} + \underbrace{\boldsymbol{\varepsilon}_i}_{\text{random}}$$

$$\boldsymbol{\varepsilon}_i \sim \boldsymbol{iid}\ N(\boldsymbol{0}, \sigma^2)$$

Independent observations with constant variance

## Linear Mixed Model

The parameters in a LMM are $\beta$ and the variances and covariances in $D$ and $R_i$

$$\boldsymbol{Y}_i = \underbrace{\boldsymbol{X}_i\boldsymbol{\beta}}_{\text{fixed}} + \underbrace{\boldsymbol{Z}_i\boldsymbol{u}_i + \boldsymbol{\varepsilon}_i}_{\text{random}}$$

$$\boldsymbol{u}_i \sim N(\boldsymbol{0}, \boldsymbol{D})$$

$$\boldsymbol{\varepsilon}_i \sim N(\boldsymbol{0}, \boldsymbol{R}_i)$$

Variance-Covariance Matrix, captures non-independence

# SYNTAX

```
PROC MIXED < options > ;
  BY variables ;
  CLASS variables ;
  ID variables ;
  MODEL dependent = < fixed-effects > < / options > ;
  RANDOM random-effects < / options > ;
  REPEATED < repeated-effect > < / options > ;
  PARMS (value-list) ... < / options > ;
  PRIOR < distribution > < / options > ;
  CONTRAST 'label' < fixed-effect values ... >  < | random-effect values ... > ,
  ... < / options > ;
  ESTIMATE 'label' < fixed-effect values ... >  < | random-effect values ... >
  < / options > ;
  LSMEANS fixed-effects < / options > ;
  WEIGHT variable;
  ODS OUTPUT 'table' OUT=SAS-data-set ;
  RUN;
```

# PROC MIXED

- METHOD= specifies the estimation methods (ML, REML)
- CLASS= specifies which variables are considered as factors (ex, TRT).
- MODEL specifies the model (i.e response and fixed effects *X*i).
- ID In general, SAS uses the same order as the original data
- RANDOM specifies the random effects (*Zi*)
  - Solution needed to calculate empirical Bayes estimates
  - Subject= id variable
  - G, gcorr, v, vcorr prints correlation matrices *D* and *Vi*
- REPEATED used to specify the Si. The repeated effects must be classification variables.
- TYPE= specifies the structure of Σ. Simple means independence.
- R and RCORR prints residual covariance, Σ, and correlation matrices.
- CONTRAST allows testing hypothesis
- ESTIMATE permits the estimation of one or several linear combinations of the fixed effects
- LSMEANS Calculates least squares mean estimates of specified fixed effects

# Importance of REPEATED

- CLASS statement sets up categorial factors for both fixed and random effects
- MODEL statement specifies fixed factors in the model
- RANDOM statement in PROC MIXED is used to model covariance in the data.
- **REPEATED** statement is more useful to find **covariance structure** of repeated measures.
- Basic Syntax of **REPEATED**:

  REPEATED <repeated factor variable> / SUB=<combination of variables>

  TYPE=<covariance structure name>(<option>);

- The effect listed before the option slash (/).
- The SUB or SUBJECT= effect defines the effect whose levels identify observations belonging to the same subject.
- The TYPE= option determines the covariance structure in Σ.

# Some important **Covariance Structures**

## TYPE=VC

- VC=Variance Components.
- Simplest (single parameter is estimated) and Default setting
- Not a reasonable choice for repeated measures designs.
- 0 covariance along off-diagonal
- Constant variance ($\sigma^2$) along diagonal

$$\begin{array}{c} Time\_1 \\ Time\_2 \\ Time\_3 \\ Time\_4 \end{array} \begin{bmatrix} \sigma^2 & 0 & 0 & 0 \\ 0 & \sigma^2 & 0 & 0 \\ 0 & 0 & \sigma^2 & 0 \\ 0 & 0 & 0 & \sigma^2 \end{bmatrix}$$

# Some important **Covariance Structures**

## TYPE=CS

- CS= Compound symmetry.
- Equal variances on diagonal
- Equal covariance along off diagonal (equal correlation)
- Simplest Structure for fitting Repeated measures
- Only 2 parameters need to be estimated
- Either RANDOM or REPEATED sentence can be used with CS structure.

$$
\begin{array}{c}
Time\_1 \\ Time\_2 \\ Time\_3 \\ Time\_4
\end{array}
\begin{bmatrix}
\sigma^2+\sigma & \sigma_1 & \sigma_1 & \sigma_1 \\
\sigma_1 & \sigma^2+\sigma & \sigma_1 & \sigma_1 \\
\sigma_1 & \sigma_1 & \sigma^2+\sigma & \sigma_1 \\
\sigma_1 & \sigma_1 & \sigma_1 & \sigma^2+\sigma
\end{bmatrix}
$$

# Some important **Covariance Structures**

## TYPE=UN

- UN= **Unstructured**.
- Most complex structure
- Variance estimated for each time, covariance for each pair of times.
- Different covariances on off-diagonal
- Different variance ($\sigma_i^2$) along diagonal
- Leads to less precise parameter estimation (degrees of freedom problem)
- Unstructured models require estimating K+K(K–1)/2 parameters
- Only REPEATED sentence can be used with **UN**.

$$
\begin{array}{r}
Time\_1 \\ Time\_2 \\ Time\_3 \\ Time\_4
\end{array}
\begin{bmatrix}
\sigma_1^2 & \sigma_{21} & \sigma_{31} & \sigma_{41} \\
\sigma_{12} & \sigma_2^2 & \sigma_{32} & \sigma_{42} \\
\sigma_{13} & \sigma_{23} & \sigma_3^2 & \sigma_{43} \\
\sigma_{14} & \sigma_{24} & \sigma_{34} & \sigma_4^2
\end{bmatrix}
$$

# Some important **Covariance Structures**

## First Order Autoregressive AR(1): TYPE= AR(1)

$$\begin{array}{c} Time\_1 \\ Time\_2 \\ Time\_3 \\ Time\_4 \end{array}\begin{bmatrix} \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 & \rho^3\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 \\ \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho^3\sigma^2 & \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 \end{bmatrix}$$

+ Equal variances on diagonal
+ Off diagonal: Variance ($\sigma^2$) multiplied by the repeated measures coefficient ($\rho$) raise to increasing powers as the observations become increasingly separated in time.
+ Times must be equally ordered and equally spaced
+ Estimates 2 parameters $\rho$ and $\sigma^2$
+ Both RANDOM and REPEATED statements can be used

# Finding suitable **Covariance Structure**

- One can estimate a number of different covariance structures
  - This is Key, Each experiment may have different covariance structure.
  - Important to know which covariance structure best fits the random variances and covariance of the data.

**Strategy / Algorithm:**

  - First run unstructured (UN)
  - Next run compound symmetry (CS) – simplest RM structure
  - Next try other covariance structures that best fit the experimental design and biology of organism
- **Use Model-Fitting Statistics**
  - AIC – Akaike's Information Criteria: (smaller is better)
  - BIC(SBC) – Schwarz's Bayesian Criteria: (smaller is better)

**Goal is to find covariance structure that is better than compound symmetry**

# Data structure for PROC MIXED: some examples

- Example 1: Arm strength is measured on 8 patients at 3 different times and where patients have been randomized to one of 2 treatment groups.
- The multivariate view associated with e.g. PROC GLM code: would look like below

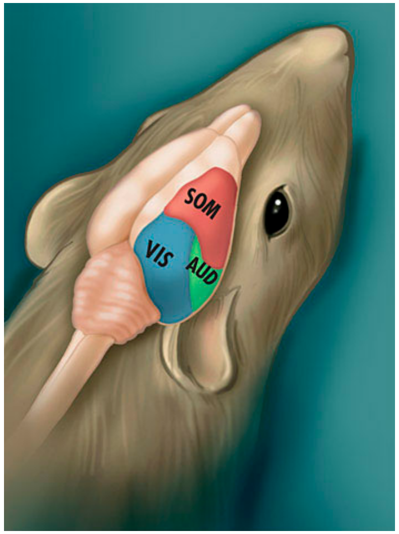
| Obs | Treatment | Subject | Time1 | Time2 | Time3 |
|---|---|---|---|---|---|
| 1 | 1 | 1 | 8 | 10 | 4 |
| 2 | 1 | 2 | 7 | 1 | 5 |
| 3 | 1 | 3 | 9 | 10 | 9 |
| 4 | 1 | 4 | 3 | 2 | 5 |
| 5 | 2 | 1 | 4 | 9 | 2 |
| 6 | 2 | 2 | 8 | 3 | 2 |
| 7 | 2 | 3 | 5 | 5 | 5 |
| 8 | 2 | 4 | 10 | 0 | 1 |

- For analysis of this data set using PROC MIXED, the univariate or stacked-data view will be required.
- The univariate view was obtained by PROC TRANSPOSE.

| Obs | Treatment | Subject | Time | Strength |
|---|---|---|---|---|
| 1 | 1 | 1 | Time1 | 8 |
| 2 | 1 | 1 | Time2 | 10 |
| 3 | 1 | 1 | Time3 | 4 |
| 4 | 1 | 2 | Time1 | 7 |
| 5 | 1 | 2 | Time2 | 1 |
| 6 | 1 | 2 | Time3 | 5 |
| 7 | 1 | 3 | Time1 | 9 |
| 8 | 1 | 3 | Time2 | 10 |
| 9 | 1 | 3 | Time3 | 9 |
| 10 | 1 | 4 | Time1 | 3 |
| 11 | 1 | 4 | Time2 | 2 |
| 12 | 1 | 4 | Time3 | 5 |
| 13 | 2 | 1 | Time1 | 4 |
| 14 | 2 | 1 | Time2 | 9 |
| 15 | 2 | 1 | Time3 | 2 |
| 16 | 2 | 2 | Time1 | 8 |
| 17 | 2 | 2 | Time2 | 3 |
| 18 | 2 | 2 | Time3 | 2 |
| 19 | 2 | 3 | Time1 | 5 |
| 20 | 2 | 3 | Time2 | 5 |
| 21 | 2 | 3 | Time3 | 5 |
| 22 | 2 | 4 | Time1 | 10 |
| 23 | 2 | 4 | Time2 | 0 |
| 24 | 2 | 4 | Time3 | 1 |

# Example: Rat Data

+ Chemical concentration in 3 different brain regions in rats




Rat 1

**Level 2**

**(Units of Analysis)**

Rat 2…

| | | | | | |
|---|---|---|---|---|---|
| Brain Region 1 | Brain Region 2 | Brain Region 3 | Brain Region 1 | Brain Region 2 | Brain Region 3 |

**Level 1 (Repeated Measures)**

# Example 3:

```
/*To illustrate Repeated measure analysis */
/*with random effect using PROC MIXED      */

DATA test;
INPUT Treatment Center Subjid Baseline Timept1 Timept2;
DATALINES;
1 1 1 22.4 63.0 56.1
1 1 2 58.0 65.4 57.7
1 1 3 50.3 63.7 81.3
1 1 4 64.9 77.0 69.5
1 2 1 51.0 56.5 77.0
1 2 2 58.8 63.0 52.3
1 2 3 62.4 57.7 79.3
1 2 4 56.2 58.3 53.3
1 3 1 17.4 25.1 65.1
1 3 2 32.7 37.8 38.9
1 3 3 14.2 29.3 44.6
1 3 4 43.0 43.6 47.4
1 4 1 55.1 85.3 66.5
1 4 2 62.0 69.4 74.1
1 4 3 62.6 69.0 64.7
1 4 4 60.1 41.7 68.3
```

```
1 5 1 61.6 71.5 52.1
1 5 2 35.8 43.8 64.4
1 5 3 48.6 73.0 76.8
1 5 4 50.4 70.9 51.5
2 1 1 48.0 51.0 65.4
2 1 2 41.2 72.8 79.4
2 1 3 35.2 53.1 55.2
2 1 4 20.1 64.7 68.9
2 2 1 39.6 65.9 68.5
2 2 2 43.0 71.1 87.0
2 2 3 67.1 66.1 92.0
2 2 4 33.9 67.3 72.4
2 3 1 51.1 69.5 77.1
2 3 2 46.1 75.4 68.4
2 3 3 63.5 75.6 78.6
2 3 4 46.3 58.8 81.6
2 4 1 50.8 60.4 71.9
2 4 2 47.7 67.8 78.8
2 4 3 46.4 59.9 66.9
2 4 4 54.2 84.2 87.9
2 5 1 50.7 82.5 65.1
2 5 2 59.0 88.1 83.7
2 5 3 80.5 97.8 94.3
2 5 4 45.5 93.4 87.8
;
RUN;
```

```
/*Step1: Create a stacked dataset and and an ID variable _N_*/
DATA TestStack;
   SET Test;
   ID = _N_;
RUN;

/*Step2: Stack the data*/
/*Create a new 'response' dependant variable and Time variable*/
DATA TestStack2;
   SET TestStack;
   Time=1; Response=Timept1; OUTPUT;
   Time=2; Response=Timept2; OUTPUT;
   DROP Timept1 Timept2;
RUN;

/*Print the dataset*/
PROC PRINT DATA=TestStack2;
RUN;
```

| Obs | Treatment | Center | Subjid | Baseline | ID | Time | Response |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 1 | 22.4 | 1 | 1 | 63.0 |
| 2 | 1 | 1 | 1 | 22.4 | 1 | 2 | 56.1 |
| 3 | 1 | 1 | 2 | 58.0 | 2 | 1 | 65.4 |
| 4 | 1 | 1 | 2 | 58.0 | 2 | 2 | 57.7 |
| 5 | 1 | 1 | 3 | 50.3 | 3 | 1 | 63.7 |
| 6 | 1 | 1 | 3 | 50.3 | 3 | 2 | 81.3 |
| 7 | 1 | 1 | 4 | 64.9 | 4 | 1 | 77.0 |
| 8 | 1 | 1 | 4 | 64.9 | 4 | 2 | 69.5 |
| 9 | 1 | 2 | 1 | 51.0 | 5 | 1 | 56.5 |
| 10 | 1 | 2 | 1 | 51.0 | 5 | 2 | 77.0 |
| 11 | 1 | 2 | 2 | 58.8 | 6 | 1 | 63.0 |
| 12 | 1 | 2 | 2 | 58.8 | 6 | 2 | 52.3 |
| 13 | 1 | 2 | 3 | 62.4 | 7 | 1 | 57.7 |
| 14 | 1 | 2 | 3 | 62.4 | 7 | 2 | 79.3 |
| 15 | 1 | 2 | 4 | 56.2 | 8 | 1 | 58.3 |
| 16 | 1 | 2 | 4 | 56.2 | 8 | 2 | 53.3 |
| 17 | 1 | 3 | 1 | 17.4 | 9 | 1 | 25.1 |
| 18 | 1 | 3 | 1 | 17.4 | 9 | 2 | 65.1 |
| 19 | 1 | 3 | 2 | 32.7 | 10 | 1 | 37.8 |
| 20 | 1 | 3 | 2 | 32.7 | 10 | 2 | 38.9 |
| 21 | 1 | 3 | 3 | 14.2 | 11 | 1 | 29.3 |
| 22 | 1 | 3 | 3 | 14.2 | 11 | 2 | 44.6 |
| 23 | 1 | 3 | 4 | 43.0 | 12 | 1 | 43.6 |
| 24 | 1 | 3 | 4 | 43.0 | 12 | 2 | 47.4 |
| 25 | 1 | 4 | 1 | 55.1 | 13 | 1 | 85.3 |
| 26 | 1 | 4 | 1 | 55.1 | 13 | 2 | 66.5 |
| 27 | 1 | 4 | 2 | 62.0 | 14 | 1 | 69.4 |
| 28 | 1 | 4 | 2 | 62.0 | 14 | 2 | 74.1 |
| 29 | 1 | 4 | 3 | 62.6 | 15 | 1 | 69.0 |
| 30 | 1 | 4 | 3 | 62.6 | 15 | 2 | 64.7 |
| 31 | 1 | 4 | 4 | 60.1 | 16 | 1 | 41.7 |
| 32 | 1 | 4 | 4 | 60.1 | 16 | 2 | 68.3 |
| 33 | 1 | 5 | 1 | 61.6 | 17 | 1 | 71.5 |
| 34 | 1 | 5 | 1 | 61.6 | 17 | 2 | 52.1 |
| 35 | 1 | 5 | 2 | 35.8 | 18 | 1 | 43.8 |
| 36 | 1 | 5 | 2 | 35.8 | 18 | 2 | 64.4 |
| 37 | 1 | 5 | 3 | 48.6 | 19 | 1 | 73.0 |
| 38 | 1 | 5 | 3 | 48.6 | 19 | 2 | 76.8 |
| 39 | 1 | 5 | 4 | 50.4 | 20 | 1 | 70.9 |
| 40 | 1 | 5 | 4 | 50.4 | 20 | 2 | 51.5 |

## The Mixed Procedure

### Estimated R Matrix for Subject 1

| Row | Col1 | Col2 |
|---|---|---|
| 1 | 104.95 | 10.5119 |
| 2 | 10.5119 | 104.95 |

### Estimated R Correlation Matrix for Subject 1

| Row | Col1 | Col2 |
|---|---|---|
| 1 | 1.0000 | 0.1002 |
| 2 | 0.1002 | 1.0000 |

### Covariance Parameter Estimates

| Cov Parm | Subject | Estimate |
|---|---|---|
| Center(Treatment) | | 21.0904 |
| CS | ID | 10.5119 |
| Residual | | 94.4387 |

### Fit Statistics

| | |
|---|---|
| -2 Res Log Likelihood | 595.7 |
| AIC (smaller is better) | 601.7 |
| AICC (smaller is better) | 602.0 |
| BIC (smaller is better) | 602.6 |

### Type 3 Tests of Fixed Effects

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| Baseline | 1 | 68 | 14.66 | 0.0003 |
| Treatment | 1 | 8 | 13.23 | 0.0066 |
| Time | 1 | 68 | 4.36 | 0.0406 |

```
/*Fit the MIXED model*/
PROC MIXED DATA = TestStack2 METHOD = REML;
  CLASS Treatment Center;
  MODEL Response = Baseline  Treatment Time;
  RANDOM Center(Treatment);
  REPEATED / SUBJECT=ID R RCORR TYPE=CS;
RUN;
```

```
/*Fit the MIXED model*/
PROC MIXED DATA = TestStack2 METHOD = REML;
  CLASS Treatment Center;
  MODEL Response = Baseline  Treatment Time;
  RANDOM Center(Treatment);
  REPEATED / SUBJECT=ID R RCORR TYPE=CS;
RUN;

NOTE: Convergence criteria met.
NOTE: PROCEDURE MIXED used (Total process time):
      real time           0.06 seconds
      cpu time            0.06 seconds
```

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The Mixed Procedure

**Estimated R Matrix for Subject 1**

| Row | Col1 | Col2 |
|---|---|---|
| 1 | 106.05 | 9.4134 |
| 2 | 9.4134 | 106.05 |

**Estimated R Correlation Matrix for Subject 1**

| Row | Col1 | Col2 |
|---|---|---|
| 1 | 1.0000 | 0.08876 |
| 2 | 0.08876 | 1.0000 |

**Covariance Parameter Estimates**

| Cov Parm | Subject | Estimate |
|---|---|---|
| Center(Treatment) | | 21.0904 |
| CS | ID | 9.4134 |
| Residual | | 96.6358 |

**Fit Statistics**

| | |
|---|---|
| -2 Res Log Likelihood | 590.8 |
| AIC (smaller is better) | 596.8 |
| AICC (smaller is better) | 597.1 |
| BIC (smaller is better) | 597.7 |

**Type 3 Tests of Fixed Effects**

| Effect | Num DF | Den DF | F Value | Pr > F |
|---|---|---|---|---|
| Baseline | 1 | 67 | 14.66 | 0.0003 |
| Treatment | 1 | 8 | 2.29 | 0.1687 |
| Time | 1 | 67 | 4.26 | 0.0430 |
| Time*Treatment | 1 | 67 | 0.11 | 0.7374 |

```
/*To Test interaction between Treatment and Time*/
PROC MIXED DATA = TestStack2 METHOD = REML;
  CLASS Treatment Center;
  MODEL Response = Baseline  Treatment Time Treatment*Time;
  RANDOM Center(Treatment);
  REPEATED / SUBJECT=ID R RCORR TYPE=CS;
RUN;
```

```
PROC MIXED DATA = TestStack2 METHOD = REML;
  CLASS Treatment Center;
  MODEL Response = Baseline  Treatment Time Treatment*Time;
  RANDOM Center(Treatment);
  REPEATED / SUBJECT=ID R RCORR TYPE=CS;
RUN;

NOTE: Convergence criteria met.
NOTE: PROCEDURE MIXED used (Total process time):
      real time           0.04 seconds
      cpu time            0.04 seconds
```

# Summary

- Repeated measures data need mixed models because of correlations between measurements on the same subject.
- Modeling the covariance structure is a preliminary step in the analysis of repeated measures data using mixed model methodology.
- In PROC GLM, repeated measures are handled in a multivariate framework and it requires a multivariate view of the data
- PROC MIXED is much more powerful than PROC GLM. Because it is more powerful, it is more complex to use.
- PROC MIXED offers greater flexibility for the modelling of repeated measures data than PROC GLM. It has a large choice of covariance structures (unstructured, compound symmetry, autoregressive, etc) for valid estimation of covariance in the data
- PROC MIXED can handle some forms of missing data without discarding an entire subject's-worth of data.

# References / acknowledgements


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- Google, SAS/STAT User's Guide, GSK notes, etc


Thank You