Lecture 19: Random Effects Model

Reading Assignment:

- Muller and Fetterman, Chapter 15: "Special Cases of Two-Way ANOVA and Random Effects" (Required)
- Littell, Milliken, Stroup, and Wolfinger. *SAS System for Mixed Models*. (Great SAS reference for longitudinal data analysis.)

Mixed effects models are an extension of the GLM for correlated data. Applications include

- clustering by center, clinic, or primary care physician,
- responses measured on individual mice in a litter,
- meta-analysis to combine the results of many different studies, and

- repeated measures over time.

In addition, factors in an experiment may be considered *fixed* or *random*. We used *fixed effects* when we wish to make inferences only about the particular k levels of the factor observed in the study. Examples include gender, treatment, or dose. We use *random effects* when these levels are a sample from a population of levels. Examples include subjects, observers, and clinic sites.

In order to decide whether a given factor should be treated as random or fixed, consider repetition of the experiment. If you repeated an experiment testing a new drug on patients in 5 Chapel Hill psychiatric clinics, what would have to be the same to make the experiment a repeat? Presumably, the second experiment should have the same drugs and doses as the first (fixed factors), but using 5 different psychiatric clinics may not really matter (random factor).

So far, we have considered models of the form

$$y = \text{fixed effects} + \text{error}.$$

The variance in y is partitioned into what can be explained by fixed effects and what remains unexplained. The error term is the only part of the right hand side of that equation that has any variance. In addition, recall that we assume for the glm that error terms are independent.

If a model contains a random factor, then we have the form

$$y = \text{fixed effects} + \text{random effects} + \text{error}.$$

The random factor also has variance, and we now partition variance into that due to fixed factors, random factors, and unexplained factors. While we assume that subjects with different levels of the random factor are independent, we allow subjects at the same level of the random factor to have correlated errors.

Introduction to Clustered Data

Multiple responses ($\mathbf{y}$'s), called *repeated measures*, are often taken per subject. If the repeated measures are recorded over time, we call these *longitudinal data*. The set of one *subject*'s repeated measures make up a *cluster*.

Clustered data do not have to be longitudinal. For example, clusters could be defined by members families participating in a genetic study or patients in medical clinics across North Carolina. In the family study, we assume subjects from different families will be independent, but that subjects within a family may be correlated.

Clustered data generally signal a violation of the homogeneity of variances assumption because subjects within a cluster are typically more alike than subjects in different clusters. Regression procedures must take into account the correlation between subjects within a cluster, and assuming falsely that observations in a cluster are

independent may give invalid results.

The correlation (dependence) structure in the data takes a specific form. Clustered data imply that observations inside a cluster (family, subject) are correlated but observations from different clusters are uncorrelated.

Longitudinal Analysis

Longitudinal studies have designs in which the outcome variable is measured repeatedly over time.

Examples include

- The ARIC (Atherosclerosis Risk in Communities) Study at CSCC, in which over 15,000 subjects were examined at baseline and every three years for a number of cardiovascular endpoints.
- A study at the CPC that monitors women during pregnancy and for one year after delivery to investigate factors related to lifetime weight gain.
- HIV clinical trials in which viral load levels are monitored throughout the course of a patient's disease.

Scientific advantages of longitudinal study designs include the following.

- Longitudinal studies allow investigation of events that occur over time, which is essential to the study of growth, aging, or the course of disease.
- Longitudinal studies allow us to study the order of events.
- Longitudinal studies permit more complete ascertainment of exposure histories in epidemiologic studies.
- Longitudinal studies can reduce unexplained variability in response by using the subject as his or her own control (crossover studies).

Randomized-blocks Experiment

Blocking is a powerful experimental design technique when the experimental subjects are heterogeneous with respect to certain variables that are associated with the response but are not of primary interest. Blocking consists of the following two steps:

1. grouping homogeneous experimental units together to form a block, and
2. assigning treatments at random to experimental units within a block.

Blocking prevents one type of subject from predominantly receiving one type of treatment. Suppose we conduct a national clinical trial of three treatments in 100 hospitals across the United States. Because we feel that patients within a hospital may be more alike than patients across hospitals (due to factors like population served by hospital, quality of nursing care in hospital, etc.), we wish to treat each hospital

as a block. Within each hospital (block), we will randomly assign the three treatments.

Components of Variance

Until now, we have considered only one variance, σ^2, in our regression models. When we use random effects, we have additional variance terms to estimate. For example, we may treat hospitals as random factors in a multi-center study if we view these hospitals as random samples from a population of US hospitals (but aren't partically interested in hospital performance). If the variance due to the hospitals is much larger than the random error, for example, then this indicates that hospitals are extremely variable, and future studies would benefit by choosing a greater number of hospitals. If hospital variance is low, then we might have saved money by recruiting more patients in fewer centers.

General Linear Mixed-Effects Model

The *general linear mixed-effects model* is often written

$$\mathbf{Y}_i = \mathbf{X}_i\boldsymbol{\beta} + \mathbf{Z}_i\mathbf{b}_i + \boldsymbol{\varepsilon}_i,$$

where $\mathbf{Y}_i$ is the vector of responses for subject i, $\mathbf{X}_i$ is the vector of fixed covariates for subject i, $\boldsymbol{\beta}$ is a p-dimensional parameter vector, $\mathbf{Z}_i$ is a matrix of known covariates, and $\mathbf{b}_i$ is a q-dimensional vector containing the random effects. We assume that $\mathbf{b}_i \sim N(\mathbf{0}, \mathbf{D})$, $\boldsymbol{\varepsilon}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma}_\mathbf{i})$, and $\mathbf{b}_1, \ldots, \mathbf{b}_n, \boldsymbol{\varepsilon}_1, \ldots, \boldsymbol{\varepsilon}_n$ are independent. This model is also commonly called the Laird-Ware model after its developers (Laird and Ware, 1982).

In BIOS 663, we will just consider $\mathbf{Z}_i$ to be indicator variables denoting cluster (e.g., family) membership, though more complicated structures are possible.

Randomized Block Design Example

Three drugs that were thought to affect lymphocyte production were included in an experiment along with a placebo drug (a control that has no physiological properties). To control for potential variation among experimental units (here, mice), it was decided to block together mice from the same litter (same mother and father and born at the same time). Five (5) litters of mice were used where four (4) mice were selected from each litter, then one of the four drugs was randomly assigned (without replacement) to each mouse within each litter. This resulted in a balanced randomized complete block design. A complete block is a block that receives all levels of the treatments. After a sufficient period of time, a blood sample was drawn from each mouse and the number of lymphocytes per cubic millimeter was determined. The data are represented as thousands of lymphocytes per cubic millimeter. The data are taken from Mead et al. (Mead, R., R.N. Curnow, and A.M. Hasted. 1993. Statistical Methods in Agriculture

and Experimental Biology. Chapman and Hall, London, p656).

Note that the randomization of assignments of drug levels to mice is performed independently for each litter. Since the drugs that are used in the experiment were purposefully selected and interest will be in the mean response of each drug it is reasonable to treat the drugs as fixed effects. The litters of mice, however, should be considered as a random effect. If the experiment were repeated again it is unlikely that these same litters would be used again. Further, interest would be in making inferences over all potential litters of mice rather than just the 5 litters used in this experiment. This randomized complete block model could be written as:

$$y_{ij} = \mu + \alpha_j + b_i + \varepsilon_{ij},$$

where $i = 1, \ldots, 5$ and $j = 1, \ldots, 4$. As usual, $\varepsilon_{ij} \sim N(0, \sigma^2)$, and we let $b_i \sim N(0, \sigma_b^2)$. y_{ij} is the lymphocyte count on the mouse in litter i receiving drug j, μ is the overall mean, α_j is the effect of the jth drug, b_i is the effect of the ith block (i.e., the ith litter), and b_i and e_{ij} are

independent random variables. Note that we have assumed that the block effect and the treatment effect do not interact. It is the investigators responsibility to select blocks appropriate for the experiment that will not interact with the treatment. If interaction is possible, then it may be better to include the "block" in the experiment as a random treatment factor and use a factorial design so that the interaction can be investigated.

As there is a control treatment in the experiment, it may be desired to make comparisons of each treatment (drug) mean with the control level to determine separately for each drug whether or not it had an effect. This might be important in a drug screening study where interest is in determining which drugs to continue to pursue, rather than comparing among drugs to determine which is best or which ones differ in thier effects. The Dunnetts multiple comparison procedure is useful in this instance. Dunnetts procedure controls the type I error rate over the family of statements of each mean to the control. Note that comparisons of this type can also be oneided comparisons as you

may only be interested in differences of means versus the control that are positive (or negative) (drug mean is larger than the control, drug mean is less than the control). PROC MIXED permits both two and one sided comparisons. For two sided comparisons the LSMEANS statement is coded as

LSMEANS effect / DUNNETTS PDIFF=CONTROL('control level value');

while the oneided comparisons are coded as

LSMEANS effect / DUNNETTS PDIFF=CONTROLU('control level value');

where treatments are expected to be higher than the control, or

LSMEANS effect / DUNNETTS PDIFF=CONTROLL('control level value');

where treatments are expected to be below the control. In this experiment we will assume that we want the drugs to enhance (increase) the production of lymphocytes so we will use the oneided, upper comparison coding. Of course, these decisions should be made

prior to performing the data analysis and should be written in as a part of the project proposal.

Before we proceed with the analysis, let's investigate some of the ways in which blocking will affect the results and our summaries of the data, and hopefully we will also gain some insight into how blocking works and when to decide to use it. First, let's compute the variance of an individual observation y_{ij}

$Var(y_{ij}) = Var(\mu + \alpha_j + b_i + e_{ij}) = Var(b_i + e_{ij}) =$
$Var(b_i) + Var(e_{ij}) + Cov(b_i, e_{ij}) = \sigma_b^2 + \sigma^2$.

From this result we can compute the variance of the means of the drugs as

$Var(\bar{y}_j) = \frac{1}{n^2} \sum_i Var(y_{ij}) = \frac{1}{n^2} \sum_i (\sigma_b^2 + \sigma^2) = \frac{1}{n}(\sigma_b^2 + \sigma^2)$

where n = 5 is the number of blocks or litters in the experiment. Now let's investigate the covariance and correlation between measurements. Note that measurements made on mice from different litters are independent as defined by our model since both random effects are independently distributed. However, mice from the same litter are not

independent as they share the common block or litter random effect.
Thus the covariance between mice on treatments (drugs) j and j'
from litter i is given by:
$Cov(y_{ij}, y_{ij'}) = Cov(\mu + \alpha_j + b_i + e_{ij}, \mu + \alpha'_j + b_i + e_{ij'})$
$= Cov(b_i + e_{ij}, b_i + e_{ij'}) = Var(b_j) = \sigma_b^2.$

```
*************************************************************
* lympho.sas *;
* *;
* To study the effects of four drugs (A, B, C, and D, where D is a
* placebo), four (4) mice from each of five (5) litters were used,
* where litters were treated as blocks. Drugs were randomly *;
* assigned to the mice within each litter. Lymphocyte counts *;
* (thousands per cubic millimeter) were measured on each mouse. *;
* *;
* Source: Mead, R., R.N. Curnow, and A.M. Hasted. 1993. Statistical
* Methods in Agriculture and Experimental Biology. Chapman *;
```

```
* and Hall, London, p656. S540.S7.M4.1993 *;
*************************************************************
Title1 Drug Effects on Lymphocyte Counts;
options ps=55 ls=80 pageno=1 nodate;
data lympho;
input drug $ litter lcytes;
label drug=drug litter=litter lcytes=lymphocyte counts;
datalines;
A 1 7.1
B 1 6.7
C 1 7.1
D 1 6.7
A 2 6.1
B 2 5.1
C 2 5.8
D 2 5.4
A 3 6.9
```

```
B 3 5.9
C 3 6.2
D 3 5.7
A 4 5.6
B 4 5.1
C 4 5.0
D 4 5.2
A 5 6.4
B 5 5.8
C 5 6.2
D 5 5.3
;

proc print data=lympho label;
run;

proc plot data=lympho;
```

```
plot lcytes*litter=* $ drug;
run;

/* Fit an RBD Model */
proc mixed data=lympho method=REML covtest;
class litter drug;
model lcytes = drug;
random litter;
lsmeans drug / adjust=dunnett pdiff=control(D);
/* compare drugs to the placebo level, oneailed test */
lsmeans drug / adjust=dunnett pdiff=controlu(D);
run;
```

```
Drug Effects on Lymphocyte Counts                          20
The Mixed Procedure
Model Information
Data Set                          WORK.LYMPHO
Dependent Variable                LCytes
```

Covariance Structure	Variance Components
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
Litter	5	1 2 3 4 5
Drug	4	A B C D

Dimensions

Covariance Parameters	2
Columns in X	5
Columns in Z	5
Subjects	1

```
Max Obs Per Subject                20

Number of Observations

Number of Observations Read                20
Number of Observations Used                20
Number of Observations Not Used             0

Iteration History

Iteration    Evaluations    -2 Res Log Like       Criterion
0                1        38.70809588
1                1        18.49496651      0.00000000
Convergence criteria met.
```


The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Estimate	Standard Error	Z Value	Pr Z
Litter	0.3869	0.2830	1.37	0.0858
Residual	0.05308	0.02167	2.45	0.0072

Fit Statistics

-2 Res Log Likelihood	18.5
AIC (smaller is better)	22.5
AICC (smaller is better)	23.4
BIC (smaller is better)	21.7

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F

Drug	3	12	11.59	0.0007

Least Squares Means

Effect	Drug	Estimate	Standard Error	DF	t Value	Pr > |t|
Drug	A	6.4200	0.2966	12	21.64	<.00
Drug	B	5.7200	0.2966	12	19.28	<.00
Drug	C	6.0600	0.2966	12	20.43	<.00
Drug	D	5.6600	0.2966	12	19.08	<.00
Drug	A	6.4200	0.2966	12	21.64	<.00
Drug	B	5.7200	0.2966	12	19.28	<.00
Drug	C	6.0600	0.2966	12	20.43	<.00
Drug	D	5.6600	0.2966	12	19.08	<.00

Differences of Least Squares Means

Standard

Effect	Drug	Drug	Estimate	Error	DF	t Value	Tails
Drug	A	D	0.7600	0.1457	12	5.22	Both
Drug	B	D	0.06000	0.1457	12	0.41	Both
Drug	C	D	0.4000	0.1457	12	2.75	Both
Drug	A	D	0.7600	0.1457	12	5.22	Upper
Drug	B	D	0.06000	0.1457	12	0.41	Upper
Drug	C	D	0.4000	0.1457	12	2.75	Upper

Differences of Least Squares Means

Effect	Drug	Drug	Adjustment	Adj P
Drug	A	D	Dunnett-Hsu	0.0006
Drug	B	D	Dunnett-Hsu	0.9543
Drug	C	D	Dunnett-Hsu	0.0448
Drug	A	D	Dunnett-Hsu	0.0003
Drug	B	D	Dunnett-Hsu	0.5844
Drug	C	D	Dunnett-Hsu	0.0224

"Screamer" Study

A study was designed to investigate different strategies for reducing disruptive vocalizations among nursing home residents with Alzheimer's disease. Each resident in the study received four treatments (3 interventions and a control). This *crossover study* (patients received all the treatments) was designed with a "washout" period between treatments so that there would be no "carryover" effects.

Study subjects were nursing home residents, and the observational units were resident responses on each treatment. There were twelve residents (clusters) aged 71-87, 11 of whom were female. We have 4 observations (treatment responses) in each cluster. We call treatment the *crossover factor*.

This study design, in which each subject serves as his/her own control, is more powerful than a study that randomizes one-fourth (or 3)

residents to one of the four treatments. The ability to make within-subject comparisons allows us to control for much person-to-person variability.

The response of interest is the percentage of 120 fifteen-second audiotape samples with vocalizations above a fixed decibel level. The four treatments (administered on different days) were a control, a stuffed teddy bear, headphones with music, and both the teddy bear and headphones with music.

We wish to know if there are any differences in the effectiveness of the treatments.

Consider the following hypothetical subset of the data.

Subject	Control	Bear	Music	Both
1	45	33	8	37
5	23	16	13	9
6	22	28	31	12
7	46	46	30	16
8	68	58	68	48
10	13	13	7	8
11	18	27	17	9
13	35	32	51	4
15	49	44	21	27
16	57	57	74	16
19	36	30	46	30
21	33	21	21	21

Using PROC MEANS in SAS, we obtain the following summary statistics.

Treatment	Mean	Std Dev
Control	37.08	16.59
Bear	33.75	14.73
Music	32.25	22.66
Both	19.75	13.35

We will again use the model

$$y_{ij} = \mu + \alpha_j + b_i + \varepsilon_{ij},$$

where $i = 1, \ldots, 12$ and $j = 1, \ldots, 4$. As usual, $\varepsilon_{ij} \sim N(0, \sigma^2)$. But how about the distribution of b_i?

Correlation

Two variables, Y_1 and Y_2, are *independent* if the conditional distribution of $Y_1 \mid Y_2$ does not depend on Y_2.

Two variables, Y_1 and Y_2, are *uncorrelated* (i.e.,not *linearly* dependent) if $E[(Y_1 - \mu_{Y_1})(Y_2 - \mu_{Y_2})] = 0$. Note that variables can be uncorrelated without being independent (e.g.,$Y_1 = (-1, 0, 1)$ and $Y_2 = (1, 0, 1)$).

Two variables are *correlated* if $E[(Y_1 - \mu_{Y_1})(Y_2 - \mu_{Y_2})] \neq 0$. The *covariance* between Y_1 and Y_2 is given by $E[(Y_1 - \mu_{Y_1})(Y_2 - \mu_{Y_2})]$. Covariance can take any value and will be dependent on the units of the variables of interest. To make it independent of the units, we can divide by the standard deviations of the two variables to obtain the

correlation, which must lie between -1 and 1:

$$\text{Corr}(Y_1, Y_2) = \frac{E[(Y_1 - \mu_{Y_1})(Y_2 - \mu_{Y_2})]}{\sigma_{Y_1}\sigma_{Y_2}}.$$

Repeated measures from the same person are usually *positively* correlated.

We use SAS to calculate the covariance and correlation matrices for the screamer study below.

```
data new;
input subject control bear music both;
cards;
1   45    33    8    37
5   23    16    13    9
6   22    28    31    12
7   46    46    30    16
8   68    58    68    48
10   13    13    7    8
11   18    27    17    9
13   35    32    51    4
```

```
15    49    44    21    27
16    57    57    74    16
19    36    30    46    30
21    33    21    21    21
;


proc corr data=new cov;
var control bear music both;
run;
```

****

The CORR Procedure

4 Variables: control bear music both

Covariance Matrix, DF = 11

	control	bear	music	both
control	275.3	223.9	251.9	160.1
bear	223.9	217.1	249.7	103.4
music	251.9	249.7	513.6	79.1

both	160.1	103.4	79.1	178.2

Simple Statistics

Variable	N	Mean	Std Dev	Sum	Minimum
control	12	37.08333	16.59386	445.00000	13.00000
bear	12	33.75000	14.73478	405.00000	13.00000
music	12	32.25000	22.66405	387.00000	7.00000
both	12	19.75000	13.34933	237.00000	4.00000

Pearson Correlation Coefficients, N = 12
Prob > |r| under H0: Rho=0

	control	bear	music
control	1.00000	0.91585	0.67000
		<.0001	0.0171
bear	0.91585	1.00000	0.74800
	<.0001		0.0051
music	0.67000	0.74800	1.00000
	0.0171	0.0051	
both	0.72281	0.52607	0.26164
	0.0079	0.0789	0.4114

We notice that the independence assumption is not valid.

Given the responses for subject i, we define the *covariance matrix* as the following symmetric matrix of variances and covariances:

$$\text{Cov}\begin{bmatrix} Y_{i1} \\ Y_{i2} \\ \vdots \\ Y_{ik} \end{bmatrix} = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \dots & \sigma_{1k} \\ \sigma_{12} & \sigma_{22} & & \sigma_{2k} \\ \vdots & & \vdots & \\ \sigma_{1k} & \sigma_{2k} & \dots & \sigma_{kk} \end{bmatrix}.$$

Note that this matrix contains $\frac{k(k+1)}{2}$ unique elements. We sometimes refer to this as an *unstructured* covariance matrix. Sometimes it is advantageous to model the covariance structure more parsimoniously (especially when there are many repeated measurements). A popular covariance matrix that allows correlation to deteriorate over time is an *autoregressive* covariance matrix. For example, the first-order autoregressive or AR(1) covariance matrix is given by

$$\text{Cov}\begin{bmatrix} Y_{i1} \\ Y_{i2} \\ \vdots \\ y_{ik} \end{bmatrix} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \dots & \rho^{k-1} \\ \rho & 1 & \rho & & \rho^{k-2} \\ \vdots & & & \vdots & \\ \rho^{k-1} & \rho^{k-2} & \dots & \rho & 1 \end{bmatrix}$$

and contains 2 parameters.

Perhaps the most popular choice for mixed-model analysis of variance assumes that the correlation between repeated measurements is due to each subject's underlying level of response. This *subject effect* is treated as a random variable in mixed-model ANOVA. For example, if the expected response to treatment is given by $E(Y_{ij}) = \mathbf{X}_{ij}\boldsymbol{\beta}$, then the response for subject i differs from the population mean by a subject effect, b_i, and a within-subject error, w_{ij}, leading to the model

$$Y_{ij} = \mathbf{X}_{ij}\boldsymbol{\beta} + b_i + w_{ij},$$

where $b_i \sim N(0, \sigma_b^2)$ and $w_{ij} \sim N(0, \sigma_w^2)$. The covariance matrix for this model has the *compound symmetry* form:

$$\text{Cov}\begin{bmatrix} Y_{i1} \\ Y_{i2} \\ \vdots \\ Y_{ik} \end{bmatrix} = \begin{bmatrix} \sigma_b^2 + \sigma_w^2 & \sigma_b^2 & \dots \sigma_b^2 & \\ \sigma_b^2 & \sigma_b^2 + \sigma_w^2 & & \sigma_b^2 \\ \vdots & & \vdots & \\ \sigma_b^2 & \sigma_b^2 & \dots & \sigma_b^2 + \sigma_w^2 \end{bmatrix}$$

and contains only 2 parameters. Although this is not valid under as wide a set of circumstances as the unrestricted covariance, at times the unrestricted covariance can contain too many parameters to estimate from the data.

It can be shown that the correlation between two subjects in the same group under the CS structure is given by $\rho = \frac{\sigma_b^2}{\sigma_b^2 + \sigma^2}$. This is known as an exchangeable correlation. In this case, the α's are fixed treatment

effects, and the b's represent each subject's own response tendency (some people may be more vocal than others, and thus their responses may tend to be high regardless of "treatment").

One option for our analysis is to use SAS PROC MIXED to extend PROC GLM and allow for our clusters of correlated observations. Here, we define the *cluster* to be the study subject. Responses across clusters, or of different subjects, are assumed to be independent. Responses within a cluster, or on an individual subject, are assumed to be correlated.

The following SAS code was used to input the data and fit the mixed effects model to control for correlation among members in a cluster.

```
data new2(keep=subject trt scream);
set new;
trt=control; scream=control; output;
trt=bear; scream=bear; output;
trt=music; scream=music; output;
trt=both; scream=both; output;
run;
```

```
proc mixed data=new2;
class subject trt;
model scream=trt/s;
repeated/type=cs subject=subject r;
contrast bear-both trt 1 -1 0 0;
contrast bear-control trt 1 0 -1 0;
contrast bear-music trt 1 0 0 -1;
contrast both-control trt 0 1 -1 0;
contrast both-music trt 0 1 0 -1;
contrast control-music trt 0 0 1 -1;
run;
```

The output is provided below.

```
                    The Mixed Procedure

                     Model Information

        Data Set                      WORK.NEW2
        Dependent Variable            scream
```

Covariance Structure	Compound Symmetry
Subject Effect	subject
Estimation Method	REML
Residual Variance Method	Profile
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Class Level Information

Class	Levels	Values
subject	12	1 5 6 7 8 10 11 13 15 16 19 21
trt	4	bear both control music

Dimensions

Covariance Parameters	2
Columns in X	5
Columns in Z	0
Subjects	12

Max Obs Per Subject	4
Observations Used	48
Observations Not Used	0
Total Observations	48

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	385.19441916	
1	1	366.18072711	0.00000000

Convergence criteria met.

Estimated R Matrix for subject 1

Row	Col1	Col2	Col3	Col4
1	296.08	178.08	178.08	178.08

2	178.08	296.08	178.08	178.08
3	178.08	178.08	296.08	178.08
4	178.08	178.08	178.08	296.08

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
CS	subject	178.08
Residual		118.01

Fit Statistics

-2 Res Log Likelihood	366.2
AIC (smaller is better)	370.2
AICC (smaller is better)	370.5
BIC (smaller is better)	371.2

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
1	19.01	<.0001

Solution for Fixed Effects

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		32.2500	4.9673	11	6.49	<.0001
trt	bear	1.5000	4.4349	33	0.34	0.7373
trt	both	-12.5000	4.4349	33	-2.82	0.0081
trt	control	4.8333	4.4349	33	1.09	0.2837
trt	music	0	.	.	.	.

Type 3 Tests of Fixed Effects

	Num	Den

Effect	DF	DF	F Value	Pr > F
trt	3	33	5.84	0.0026

Contrasts

Label	Num DF	Den DF	F Value	Pr > F
bear-both	1	33	9.97	0.0034
bear-control	1	33	0.56	0.4576
bear-music	1	33	0.11	0.7373
both-control	1	33	15.28	0.0004
both-music	1	33	7.94	0.0081
control-music	1	33	1.19	0.2837

We see that the treatments are indeed different. Specifically, the teddy bear and music together are significantly better than all the other treatments.

SAS code and output for PROC MIXED with the UN structure are given below.

```
proc mixed data=new2 dfbw noclprint;
class subject trt;
model sbp=trt/s;
repeated/type=un subject=subject r;
contrast bear-both trt 1 -1 0 0;
contrast bear-control trt 1 0 -1 0;
contrast bear-music trt 1 0 0 -1;
contrast both-control trt 0 1 -1 0;
contrast both-music trt 0 1 0 -1;
contrast control-music trt 0 0 1 -1;
run;
```

```
*************************************************************************

                          The Mixed Procedure

                           Model Information
                    Data Set                     WORK.NEW2
                    Dependent Variable           scream
                    Covariance Structure         Unstructured
```

Subject Effect	subject
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Dimensions

Covariance Parameters	10
Columns in X	5
Columns in Z	0
Subjects	12
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	48
Number of Observations Used	48
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	385.19441916	
1	1	340.32444257	0.00000000

Convergence criteria met.

Estimated R Matrix for subject 1

Row	Col1	Col2	Col3	Col4
1	275.36	223.93	251.98	160.11
2	223.93	217.11	249.80	103.48
3	251.98	249.80	513.66	79.1591
4	160.11	103.48	79.1591	178.20

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	subject	275.36
UN(2,1)	subject	223.93

UN(2,2)	subject	217.11
UN(3,1)	subject	251.98
UN(3,2)	subject	249.80
UN(3,3)	subject	513.66
UN(4,1)	subject	160.11
UN(4,2)	subject	103.48
UN(4,3)	subject	79.1591
UN(4,4)	subject	178.20

Fit Statistics

-2 Res Log Likelihood	340.3
AIC (smaller is better)	360.3
AICC (smaller is better)	367.0
BIC (smaller is better)	365.2

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
9	44.87	<.0001

Solution for Fixed Effects

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		32.25	6.54	11	4.93	0.0005
trt	bear	1.50	4.38	11	0.34	0.7390
trt	both	-12.50	6.66	11	-1.87	0.0876
trt	control	4.83	4.87	11	0.99	0.3427
trt	music	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	3	11	11.70	0.0010

The Mixed Procedure

Contrasts

Label	Num DF	Den DF	F Value	Pr > F
bear-both	1	11	12.49	0.0047
bear-control	1	11	2.99	0.1118
bear-music	1	11	0.12	0.7390
both-control	1	11	27.04	0.0003
both-music	1	11	3.51	0.0876
control-music	1	11	0.98	0.3427

We can check whether the compound symmetry assumption is valid for the screamer data by comparing the residual log likelihoods from the compound symmetry and unrestricted covariance models.

To test the adequacy of the compound symmetry assumption, we consider a chi-squared test of the difference between the two residual log likelihoods. Recall that the compound symmetric covariance estimates 2 parameters, while the unstructured covariance estimates $\frac{4(5)}{2} = 10$ parameters.

	UN	CS
-2 Res Log L	340.3	366.2
df	1	9

Thus we compare -2 log likelihood ratio=(366.2-340.3)=25.9 to the chi-squared distribution with 8 df (which has critical value 15.5) and therefore reject the null hypothesis that the smaller model (compound

symmetry) is valid. We conclude that the compound symmetry assumption is not valid for the data.

Parallel Groups Repeated Measures Design

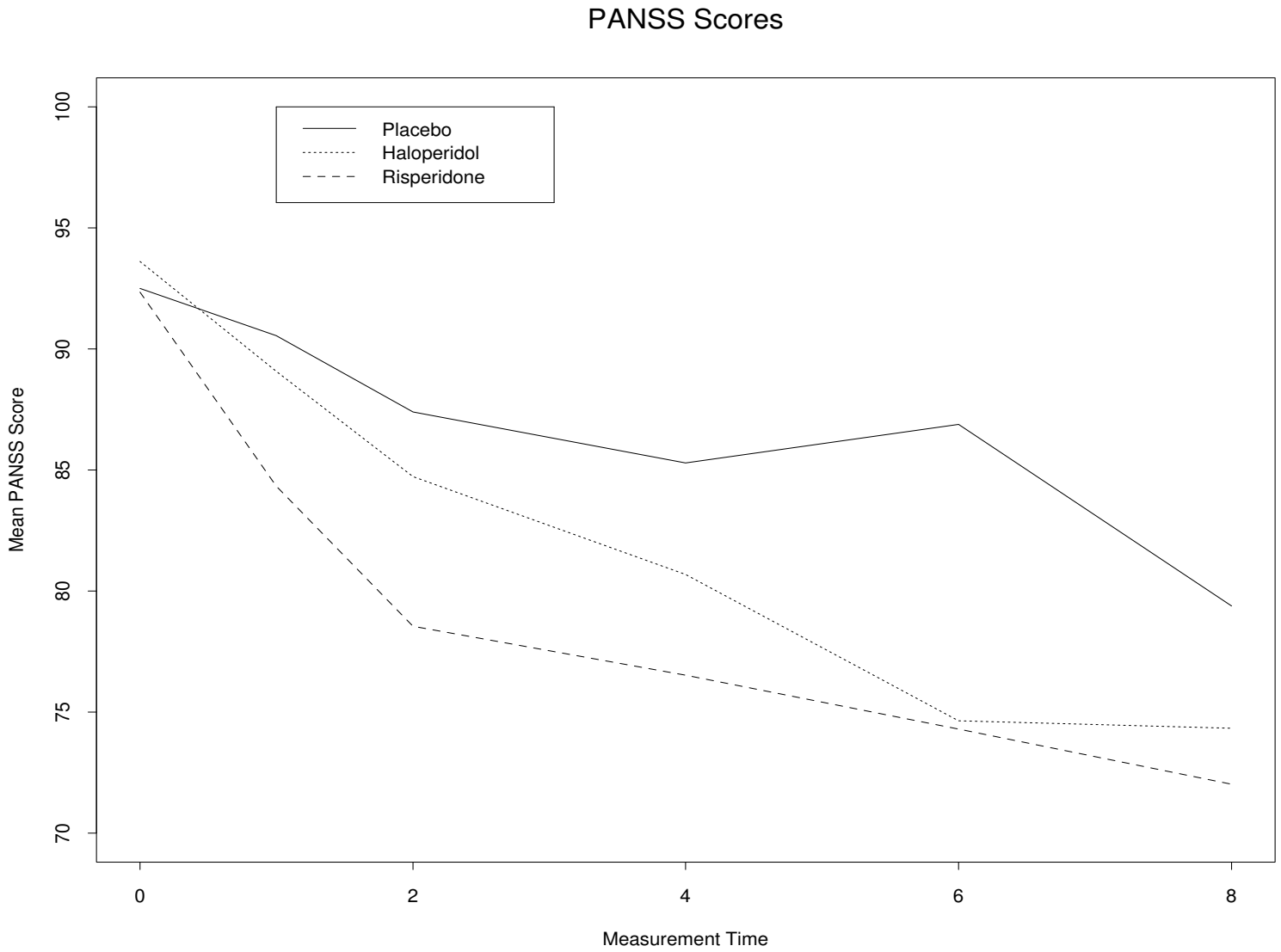
In the parallel groups design, two or more groups of subjects are measured repeatedly over time. For example, groups may be defined by *randomization* to one of several treatments.

We consider designs in which all subjects are meant to be measured at the same set of follow-up times, but these methods will allow for certain types of missing data.

The analysis goal is to characterize the patterns of change over time in the groups and to determine whether the patterns differ in the groups.

Example: Schizophrenia Clinical Trial

A multi-center study was conducted to assess the effect of two treatments and a placebo on decreasing the PANSS (positive and negative symptom scale) score. Patients were randomized to receive only one of the two treatments (haloperidol and risperidone) or a placebo. Measurements of the PANSS were taken at baseline and after 1, 2, 4, 6, and 8 weeks of treatment. Consider the following plot of PANSS score means at each measurement time. What do you think about the patterns of change over time?


PANSS Scores
Placebo
Haloperidol
Risperidone
Mean PANSS Score
100
95
90
85
80
75
70
0
2
4
6
8
Measurement Time

Notice that since this is a randomized study, the group means should be the same at baseline, so any test of treatment effect is essentially a test of treatment by time interaction (we cannot have parallel lines if there really is a treatment effect, since parallel lines would imply coincident lines in this case).

In the analysis of parallel groups data, we may have one or more of the following hypotheses.

- H_0: Are the profiles of the means similar in the three groups? (That is, are the line segments between adjacent measurement occasions parallel?) This hypothesis is the hypothesis of no group by time interaction.
- H_0: If the profiles are parallel, are they also at the same level? This is the hypothesis of no group effect. (In a randomized study, the profiles should all start at the same level.)
- H_0: If the profiles are parallel, are the means constant over time? This is the hypothesis of no time effect.

The appropriate hypotheses for any given dataset must be derived from the relevant scientific issues in that study. For example, we are interested only in the

first and last hypotheses for this randomized study. (Why?)

Notation for Parallel Groups Repeated Measures

Changing notation slightly, let n be the number of subjects (clusters) and N be the total number of observations. We consider the univariate representation (one row for each observation of the outcome) of the multivariate data.

If there are k measurement occasions, we define $k-1$ indicator variables. For the i^{th} observation, we let $x_{ij} = 1$ if the observation was taken at time j and 0 otherwise, $j = 1, \ldots, k-1$. In addition, let x_{ik} be the indicator variable for the haloperidol group and $x_{i,k+1}$ be the indicator variable for the placebo group. (Risperidone is the reference group for treatment.)

We also define $2(k-1)$ interaction terms as products of the time and group indicator variables. With these terms in the model, our model has $1 + (k-1) + (2) + 2(k-1) = 3k$ parameters for the mean model. If we use an unrestricted covariance matrix, we have $\frac{6(7)}{2} = 21$ additional parameters for the covariance.

If we let i index all the responses, $i = 1, \ldots, N$, then the model is given by

$$\begin{aligned} y_i &= \beta_0 + \beta_1 x_{i1} + \beta_2 x_{i2} + \beta_3 x_{i3} + \beta_4 x_{i4} + \beta_5 x_{i5} \\ &\quad + \beta_6 x_{i6} + \beta_7 x_{i7} + \beta_8 x_{i8} + \beta_9 x_{i9} + \beta_{10} x_{i10} \\ &\quad + \beta_{11} x_{i11} + \beta_{12} x_{i12} + \beta_{13} x_{i13} + \beta_{14} x_{i14} \\ &\quad + \beta_{15} x_{i15} + \beta_{16} x_{i16} + \beta_{17} x_{i17} + \varepsilon_i, \end{aligned}$$

where

- $x_{i1}, \ldots x_{i5}$ represent measurement times 0, 1, 2, 4, and 6 (with time 8 as the reference),
- x_{i6} and x_{i7} are the indicator variables for haloperidol and placebo, respectively (risperidone is the reference),
- $x_{i8}, \ldots, x_{i12}$ are the interactions between haloperidol and time, and
- $x_{i13}, \ldots, x_{i17}$ are the interactions between placebo and time.

Assumptions of the Parallel Groups Model

1. The subjects are random samples from each of the groups.
2. Observations from different individuals are independent, while repeated measurements on the same individual are not assumed to be independent.
3. The vector of outcomes for a given subject has a multivariate normal distribution.
4. The expected values of the individual observations are given by the linear regression model.
5. If observations are missing, they are missing at random (MAR).

Example: Schizophrenia Data

The following SAS code may be used to fit this model to the schizophrenia data (assuming the data are already in univariate format). Included are statements necessary to estimate differences in cell means for various time and treatment combinations. Note the ordering of the contrast coefficients. The first six coefficients represent haloperidol (TRT=1) at the six times (in numerical order). The next six coefficients represent placebo (TRT=2) at the six times, and the last six coefficients represent risperidone. The "e" option instructs SAS to print information about the contrast coefficients so that you can check to be sure you coded them properly (always a good idea!).

```
proc mixed data=new2 noclprint;
class id trtnew time t;
model y=trtnew time time*trtnew/s;
repeated t/type=un subject=id r;
estimate time 1 vs. baseline haloperidol1 - diff for placebo
        time*trtnew -1 1 0 0 0 0 1 -1 0 0 0 0 0 0 0 0 0 0/e;
estimate time 1 vs. baseline placebo - diff for risperidone
        time*trtnew 0 0 0 0 0 0 1 -1 0 0 0 0 -1 1 0 0 0 0/e;
estimate time 2 vs. baseline haloperidol1 - diff for placebo
        time*trtnew -1 0 1 0 0 0 1 0 -1 0 0 0 0 0 0 0 0 0/e;
```

```
estimate time 2 vs. baseline placebo - diff for risperidone
        time*trtnew 0 0 0 0 0 0 1 0 -1 0 0 0 -1 0 1 0 0 0/e;
estimate time 4 vs. baseline haloperidol1 - diff for placebo
        time*trtnew -1 0 0 1 0 0 1 0 0 -1 0 0 0 0 0 0 0 0/e;
estimate time 4 vs. baseline placebo - diff for risperidone
        time*trtnew 0 0 0 0 0 0 1 0 0 -1 0 0 -1 0 0 1 0 0/e;
estimate time 6 vs. baseline haloperidol1 - diff for placebo
        time*trtnew -1 0 0 0 1 0 1 0 0 0 -1 0 0 0 0 0 0 0 0/e;
estimate time 6 vs. baseline placebo - diff for risperidone
        time*trtnew 0 0 0 0 0 0 1 0 0 0 -1 0 -1 0 0 0 1 0/e;
estimate time 8 vs. baseline haloperidol1 - diff for placebo
        time*trtnew -1 0 0 0 0 1 1 0 0 0 0 -1 0 0 0 0 0 0 0/e;
estimate time 8 vs. baseline placebo - diff for risperidone
        time*trtnew 0 0 0 0 0 0 1 0 0 0 0 -1 -1 0 0 0 0 1/ e;
run;
```

Selected SAS output is provided below.

```
The Mixed Procedure

                        Model Information

        Data Set                        WORK.NEW2
```

Dependent Variable	y
Covariance Structure	Unstructured
Subject Effect	id
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Dimensions

Covariance Parameters	21
Columns in X	28
Columns in Z	0
Subjects	523
Max Obs Per Subject	6
Observations Used	2468
Observations Not Used	670
Total Observations	3138

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	21961.16171710	
1	2	20151.85618890	0.00610058
2	1	20096.23405069	0.00167392
3	1	20080.65977798	0.00027233
4	1	20078.27196287	0.00001373
5	1	20078.16116305	0.00000004
6	1	20078.16081868	0.00000000

Convergence criteria met.

Estimated R Matrix for id 1

Row	Col1	Col2
1	356.09	238.69
2	238.69	507.39

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	id	356.09
UN(2,1)	id	250.92
UN(2,2)	id	429.79
UN(3,1)	id	238.69
UN(3,2)	id	382.01
UN(3,3)	id	507.39
UN(4,1)	id	229.26
UN(4,2)	id	361.56
UN(4,3)	id	451.91
UN(4,4)	id	571.64
UN(5,1)	id	216.73
UN(5,2)	id	340.27
UN(5,3)	id	432.90
UN(5,4)	id	515.10
UN(5,5)	id	630.37
UN(6,1)	id	193.48
UN(6,2)	id	317.84

UN(6,3)	id	396.08
UN(6,4)	id	484.38
UN(6,5)	id	562.16
UN(6,6)	id	625.87

Fit Statistics

-2 Res Log Likelihood	20078.2
AIC (smaller is better)	20120.2
AICC (smaller is better)	20120.5
BIC (smaller is better)	20209.6

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
20	1883.00	<.0001

Solution for Fixed Effects

Effect	trtnew	time	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			78.6367	1.5171	519	51.83	<.0001
trtnew	1		6.9346	3.5402	519	1.96	0.0507
trtnew	2		17.0886	3.7912	519	4.51	<.0001
trtnew	3		0	.	.	.	.

The Mixed Procedure

Solution for Fixed Effects

Effect	trtnew	time	Estimate	Standard Error	DF	t Value	Pr > |t|
time		0	13.8419	1.4886	519	9.30	<.0001
time		1	5.6702	1.3052	519	4.34	<.0001
time		2	1.8247	1.2063	519	1.51	0.1310
time		4	0.9563	1.0284	519	0.93	0.3529
time		6	0.1495	0.8046	519	0.19	0.8527
time		8	0	.	.	.	.
trtnew*time	1	0	-5.8040	3.4774	519	-1.67	0.0957

trtnew*time	1	1	-2.1313	3.0885	519	-0.69	0.4905
trtnew*time	1	2	-0.09359	2.8842	519	-0.03	0.9741
trtnew*time	1	4	-0.2524	2.4959	519	-0.10	0.9195
trtnew*time	1	6	-0.2067	1.9499	519	-0.11	0.9156
trtnew*time	1	8	0	.	.	.	.
trtnew*time	2	0	-17.0786	3.7332	519	-4.57	<.0001
trtnew*time	2	1	-10.6730	3.3797	519	-3.16	0.0017
trtnew*time	2	2	-6.6133	3.1757	519	-2.08	0.0378
trtnew*time	2	4	-3.9971	2.7871	519	-1.43	0.1521
trtnew*time	2	6	2.4792	2.2450	519	1.10	0.2700
trtnew*time	2	8	0	.	.	.	.
trtnew*time	3	0	0	.	.	.	.
trtnew*time	3	1	0	.	.	.	.
trtnew*time	3	2	0	.	.	.	.
trtnew*time	3	4	0	.	.	.	.
trtnew*time	3	6	0	.	.	.	.
trtnew*time	3	8	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trtnew	2	519	10.96	<.0001
time	5	519	8.20	<.0001
trtnew*time	10	519	3.68	<.0001

Coefficients for time 1 vs. baseline
haloperidol1 - diff for placebo

Effect	trtnew	time	Row1
Intercept			
trtnew	1		
trtnew	2		
trtnew	3		
time		0	

The Mixed Procedure

Coefficients for time 1 vs. baseline
haloperidol1 - diff for placebo

Effect	trtnew	time	Row1
time		1	
time		2	
time		4	
time		6	
time		8	
trtnew*time	1	0	-1
trtnew*time	1	1	1
trtnew*time	1	2	
trtnew*time	1	4	
trtnew*time	1	6	
trtnew*time	1	8	
trtnew*time	2	0	1
trtnew*time	2	1	-1
trtnew*time	2	2	
trtnew*time	2	4	
trtnew*time	2	6	
trtnew*time	2	8	
trtnew*time	3	0	

```
trtnew*time    3         1
trtnew*time    3         2
trtnew*time    3         4
trtnew*time    3         6
trtnew*time    3         8


 Coefficients for time 1 vs. baseline
    placebo - diff for risperidone

Effect         trtnew    time      Row1

Intercept
trtnew         1
trtnew         2
trtnew         3
time                     0
time                     1
time                     2
time                     4
time                     6
time                     8
trtnew*time    1         0
```

```
trtnew*time    1         1
trtnew*time    1         2
trtnew*time    1         4
trtnew*time    1         6
trtnew*time    1         8

          The Mixed Procedure

 Coefficients for time 1 vs. baseline
    placebo - diff for risperidone

Effect         trtnew    time      Row1

trtnew*time    2         0            1
trtnew*time    2         1           -1
trtnew*time    2         2
trtnew*time    2         4
trtnew*time    2         6
trtnew*time    2         8
trtnew*time    3         0           -1
trtnew*time    3         1            1
trtnew*time    3         2
trtnew*time    3         4
```

```
                trtnew*time    3         6
                trtnew*time    3         8


.....some output omitted.....
```

Estimates

Label	Estimate
time 1 vs. baseline haloperidol1 - diff for placebo	-2.7329
time 1 vs. baseline placebo - diff for risperidone	-6.4056
time 2 vs. baseline haloperidol1 - diff for placebo	-4.7549

Estimates

Label	Standard Error	DF
time 1 vs. baseline haloperidol1 - diff for placebo	2.5776	519
time 1 vs. baseline placebo - diff for risperidone	2.0356	519
time 2 vs. baseline haloperidol1 - diff for placebo	3.1184	519

Estimates

Label	t Value	Pr > |t|
time 1 vs. baseline haloperidol1 - diff for placebo	-1.06	0.2895

```
time 1 vs. baseline placebo - diff for risperidone     -3.15    0.0017
time 2 vs. baseline haloperidol1 - diff for placebo    -1.52    0.1279
```

The Mixed Procedure

Estimates

Label	Estimate
time 2 vs. baseline placebo - diff for risperidone	-10.4653
time 4 vs. baseline haloperidol1 - diff for placebo	-7.5298
time 4 vs. baseline placebo - diff for risperidone	-13.0814
time 6 vs. baseline haloperidol1 - diff for placebo	-13.9604
time 6 vs. baseline placebo - diff for risperidone	-19.5578
time 8 vs. baseline haloperidol1 - diff for placebo	-11.2746
time 8 vs. baseline placebo - diff for risperidone	-17.0786

Estimates

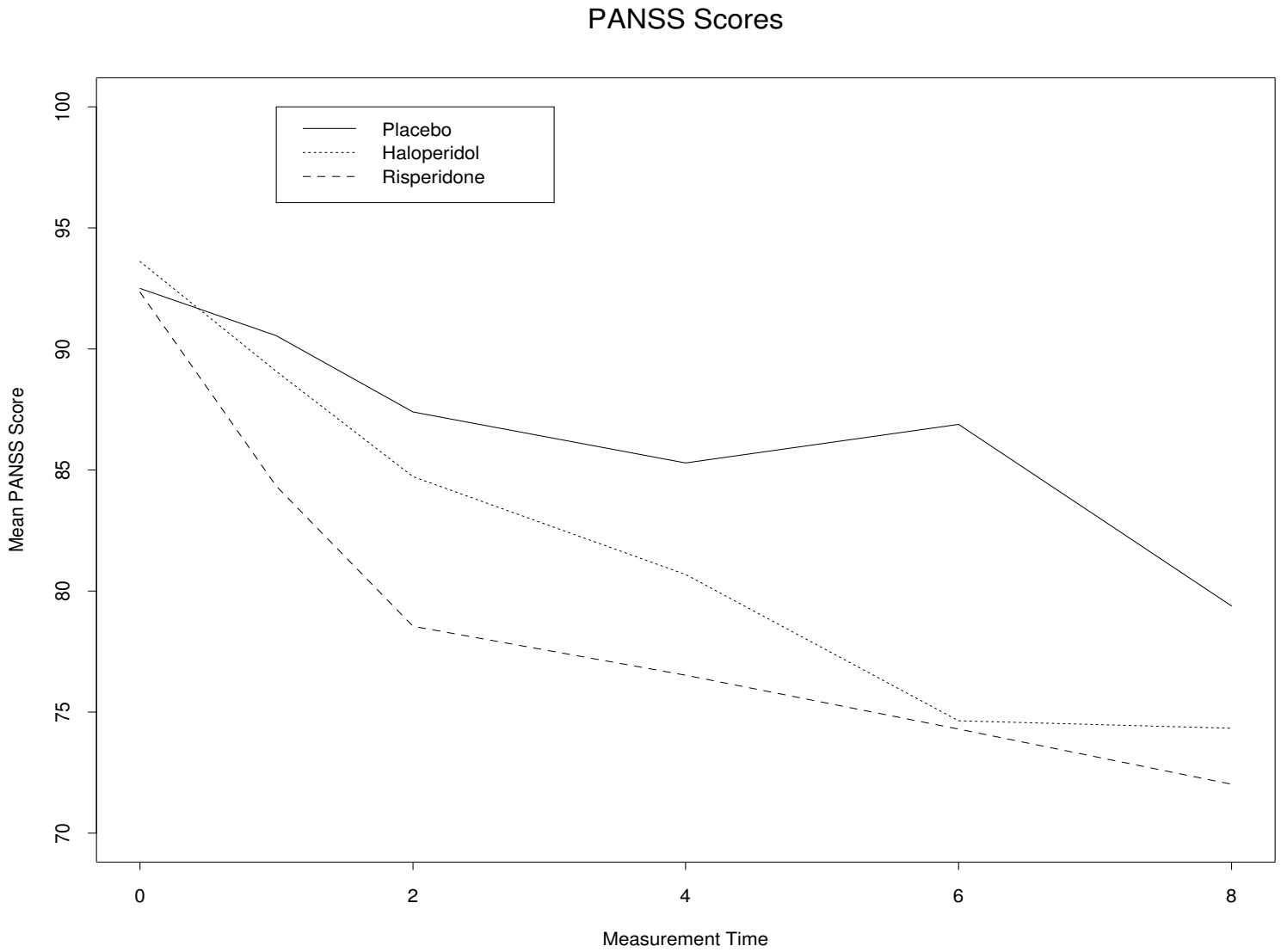
Label	Standard Error	DF

```
time 2 vs. baseline placebo - diff for risperidone     2.4715    519
time 4 vs. baseline haloperidol1 - diff for placebo    3.5989    519
time 4 vs. baseline placebo - diff for risperidone     2.8744    519
time 6 vs. baseline haloperidol1 - diff for placebo    4.2460    519
time 6 vs. baseline placebo - diff for risperidone     3.3765    519
time 8 vs. baseline haloperidol1 - diff for placebo    4.6473    519
time 8 vs. baseline placebo - diff for risperidone     3.7332    519
```

Estimates

Label	t Value	Pr > |t|
time 2 vs. baseline placebo - diff for risperidone	-4.23	<.0001
time 4 vs. baseline haloperidol1 - diff for placebo	-2.09	0.0369
time 4 vs. baseline placebo - diff for risperidone	-4.55	<.0001
time 6 vs. baseline haloperidol1 - diff for placebo	-3.29	0.0011
time 6 vs. baseline placebo - diff for risperidone	-5.79	<.0001
time 8 vs. baseline haloperidol1 - diff for placebo	-2.43	0.0156
time 8 vs. baseline placebo - diff for risperidone	-4.57	<.0001

What do we conclude based on the hypothesis tests given in the SAS output?


PANSS Scores
Placebo
Haloperidol
Risperidone
Mean PANSS Score
100
95
90
85
80
75
70
0
2
4
6
8
Measurement Time

Using the following SAS code and partial output, test whether the compound symmetry covariance is defensible for these data.

```
proc mixed data=new2 noclprint;
class id trtnew time t;
model y=trtnew time time*trtnew/s;
repeated t/type=cs subject=id r;
run;
```

```
*************************************************************************
                        The Mixed Procedure

                         Model Information

        Data Set                          WORK.NEW2
        Dependent Variable                y
        Covariance Structure              Compound Symmetry
        Subject Effect                    id
        Estimation Method                 REML
        Residual Variance Method          Profile
        Fixed Effects SE Method           Model-Based
        Degrees of Freedom Method         Between-Within
```

Dimensions

Covariance Parameters	2
Columns in X	28
Columns in Z	0
Subjects	523
Max Obs Per Subject	6
Observations Used	2468
Observations Not Used	670
Total Observations	3138

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	21961.16171710	
1	2	20548.58902724	0.00002967
2	1	20548.34199238	0.00000011
3	1	20548.34114692	0.00000000

Convergence criteria met.

Estimated R Matrix for id 1

Row	Col1	Col2
1	455.62	302.14
2	302.14	455.62

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
CS	id	302.14
Residual		153.48

The Mixed Procedure

Fit Statistics

-2 Res Log Likelihood	20548.3
AIC (smaller is better)	20552.3

```
AICC (smaller is better)      20552.3
BIC (smaller is better)       20560.9
```

Treating Time as a Continuous Variable

If the means tend to change linearly over time, we may wish to treat time as a continuous variable rather than as a categorical variable. If means do change linearly with time, then the treatment effect in a continuous-time model is captured in one single parameter, leading to more powerful tests.

If time is treated as continuous, the model is given by

$$y_i = \beta_0 + \beta_1 X_{i1} + \beta_2 X_{i2} + \beta_3 X_{i3} + \beta_4 X_{i4} + \beta_5 X_{i5} + \varepsilon_i,$$

where

- X_{i1} represents measurement time as a continuous variable taking the values 0, 1, 2, 4, 6, or 8,
- X_{i2} and X_{i3} are the indicator variables for haloperidol and placebo, respectively,
- X_{i4} is the interaction between haloperidol and time, and

- X_{i5} is the interaction between placebo and time.

To fit this model, we remove TIME from the class statement and use the following SAS code.

```
proc mixed data=new2 noclprint;
class id trtnew t;
model y=trtnew time time*trtnew/s;
repeated t/type=un subject=id r;
run;
```

Note that we still need the variable "t" (which takes the same values as "time") declared as a class variable so that we can tell SAS how the repeated measures are ordered within a subject. This is why we define two variables, "t" and "time," with the same values (if we wish to treat time as continuous, we still need a version of that variable that can be treated as a class variable).

For subjects on haloperidol, we have

$$E(Y_i) = (\beta_0 + \beta_2) + (\beta_1 + \beta_4)TIME_i,$$

for subjects on placebo, we have

$$E(Y_i) = (\beta_0 + \beta_3) + (\beta_1 + \beta_5)TIME_i,$$

and for subjects on risperidone we have

$$E(Y_i) = \beta_0 + \beta_1 TIME_i.$$

Clearly, the model assumes each group's mean changes linearly over time.

Selecting a Method for Parameterizing Time

Because fitting time as a class variable is equivalent to fitting a polynomial of order 5 in time, we can view the continuous time parameterization as a model nested in the categorical time parameterization. Thus a likelihood ratio test is appropriate for comparing the two models.

Using the following SAS code and selected output, test whether the continuous time model is appropriate for the schizophrenia data.

```
proc mixed data=new2 noclprint method=ml;
class id trtnew time t;
model y=trtnew time time*trtnew/s;
repeated t/type=un subject=id r;
run;

proc mixed data=new2 noclprint method=ml;
class id trtnew t;
model y=trtnew time time*trtnew/s;
repeated t/type=un subject=id r;
run;
```

```
**********************************************************************
                          The Mixed Procedure
```

Model Information

Data Set	WORK.NEW2
Dependent Variable	y
Covariance Structure	Unstructured
Subject Effect	id
Estimation Method	ML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Dimensions

Covariance Parameters	21
Columns in X	28
Columns in Z	0
Subjects	523
Max Obs Per Subject	6
Observations Used	2468
Observations Not Used	670
Total Observations	3138

Iteration History

Iteration	Evaluations	-2 Log Like	Criterion
0	1	22020.87344360	
1	3	20159.01391755	0.00575612
2	2	20128.62705395	0.00065058
3	1	20123.02179920	0.00003529
4	1	20122.73459148	0.00000018
5	1	20122.73319055	0.00000000

Convergence criteria met.

Estimated R Matrix for id 1

Row	Col1	Col2
1	354.04	237.31
2	237.31	504.31

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	id	354.04
UN(2,1)	id	249.48
UN(2,2)	id	427.29
UN(3,1)	id	237.31
UN(3,2)	id	379.79
UN(3,3)	id	504.31
UN(4,1)	id	227.95
UN(4,2)	id	359.46
UN(4,3)	id	449.18
UN(4,4)	id	567.96
UN(5,1)	id	215.48
UN(5,2)	id	338.29
UN(5,3)	id	430.28
UN(5,4)	id	511.81

UN(5,5)	id	625.86
UN(6,1)	id	192.37
UN(6,2)	id	315.99
UN(6,3)	id	393.69
UN(6,4)	id	481.27
UN(6,5)	id	558.20
UN(6,6)	id	621.01

Fit Statistics

-2 Log Likelihood	20122.7
AIC (smaller is better)	20200.7
AICC (smaller is better)	20202.0
BIC (smaller is better)	20366.9

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
20	1898.14	<.0001

Solution for Fixed Effects

Effect	trtnew	time	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			78.6367	1.5109	519	52.05	<.0001
trtnew	1		6.9346	3.5253	519	1.97	0.0497
trtnew	2		17.0886	3.7749	519	4.53	<.0001
trtnew	3		0	.	.	.	.

The Mixed Procedure

Solution for Fixed Effects

Effect	trtnew	time	Estimate	Standard Error	DF	t Value	Pr > |t|
time		0	13.8420	1.4824	519	9.34	<.0001
time		1	5.6703	1.2993	519	4.36	<.0001
time		2	1.8247	1.2006	519	1.52	0.1292
time		4	0.9563	1.0231	519	0.93	0.3504
time		6	0.1495	0.8002	519	0.19	0.8518

time		8	0	.	.	.	.
trtnew*time	1	0	-5.8040	3.4627	519	-1.68	0.0943
trtnew*time	1	1	-2.1313	3.0743	519	-0.69	0.4885
trtnew*time	1	2	-0.09356	2.8704	519	-0.03	0.9740
trtnew*time	1	4	-0.2524	2.4830	519	-0.10	0.9191
trtnew*time	1	6	-0.2067	1.9392	519	-0.11	0.9152
trtnew*time	1	8	0	.	.	.	.
trtnew*time	2	0	-17.0786	3.7169	519	-4.59	<.0001
trtnew*time	2	1	-10.6729	3.3639	519	-3.17	0.0016
trtnew*time	2	2	-6.6133	3.1602	519	-2.09	0.0369
trtnew*time	2	4	-3.9971	2.7726	519	-1.44	0.1500
trtnew*time	2	6	2.4792	2.2327	519	1.11	0.2673
trtnew*time	2	8	0	.	.	.	.
trtnew*time	3	0	0	.	.	.	.
trtnew*time	3	1	0	.	.	.	.
trtnew*time	3	2	0	.	.	.	.
trtnew*time	3	4	0	.	.	.	.
trtnew*time	3	6	0	.	.	.	.
trtnew*time	3	8	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trtnew	2	519	11.03	<.0001
time	5	519	8.25	<.0001
trtnew*time	10	519	3.71	<.0001

The Mixed Procedure

Model Information

Data Set	WORK.NEW2
Dependent Variable	y
Covariance Structure	Unstructured
Subject Effect	id
Estimation Method	ML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Dimensions

Covariance Parameters	21
Columns in X	8
Columns in Z	0
Subjects	523
Max Obs Per Subject	6
Observations Used	2468
Observations Not Used	670
Total Observations	3138

Iteration History

Iteration	Evaluations	-2 Log Like	Criterion
0	1	22063.13468076	
1	3	20255.08219146	0.00579452
2	2	20224.45097439	0.00070989
3	1	20218.22109780	0.00004441
4	1	20217.85586897	0.00000028
5	1	20217.85369080	0.00000000

Convergence criteria met.

Estimated R Matrix for id 1

Row	Col1	Col2
1	357.07	227.20
2	227.20	553.82

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	id	357.07
UN(2,1)	id	240.70
UN(2,2)	id	442.31
UN(3,1)	id	227.20
UN(3,2)	id	410.52

UN(3,3)	id	553.82
UN(4,1)	id	218.99
UN(4,2)	id	380.37
UN(4,3)	id	485.04
UN(4,4)	id	592.86
UN(5,1)	id	206.63
UN(5,2)	id	342.41
UN(5,3)	id	443.17
UN(5,4)	id	514.05
UN(5,5)	id	613.21
UN(6,1)	id	184.15
UN(6,2)	id	307.33
UN(6,3)	id	387.60
UN(6,4)	id	465.04
UN(6,5)	id	530.13
UN(6,6)	id	584.45

Fit Statistics

-2 Log Likelihood	20217.9
AIC (smaller is better)	20271.9
AICC (smaller is better)	20272.5

BIC (smaller is better) 20386.9

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
20	1845.28	<.0001

Solution for Fixed Effects

Effect	trtnew	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		90.0941	0.9663	519	93.24	<.0001
trtnew	1	2.3082	2.1578	519	1.07	0.2852
trtnew	2	1.5762	2.1491	519	0.73	0.4636
trtnew	3	0	.	.	.	.
time		-1.2618	0.1713	519	-7.37	<.0001
time*trtnew	1	0.4097	0.4057	519	1.01	0.3130
time*trtnew	2	1.7698	0.4404	519	4.02	<.0001
time*trtnew	3	0	.	.	.	.

The Mixed Procedure

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trtnew	2	519	0.71	0.4911
time	1	519	7.83	0.0053
time*trtnew	2	519	8.14	0.0003

Summary

When analyzing data from the parallel groups repeated measures design, consider the following strategy.

1. Choose a working covariance structure. (Note that the choice of the mean model and the covariance structure are interdependent.) Use the REML (default) log-likelihood as the criterion for selecting a covariance structure. As a general rule of thumb, the unstructured model should be used unless a simpler covariance structure is clearly satisfactory. (**Restricted (residual) maximum likelihood (REML)**: REML is an alternative to full maximum likelihood estimation and is typically the default method in most statistical packages. Rather than maximizing the likelihood of the data, it maximizes the likelihood of the observed residuals. REML obtains initial estimates of the fixed effects using ordinary least squares and then using these estimates it maximizes the likelihood of the residuals (in which the fixed effects are subtracted off) to obtain estimates of the variance parameters. Finally the estimated variance parameters are used to obtain generalized least squares estimates of the fixed effect parameters. REML is a good alternative to

ML when the sole focus is on estimation of the variance components. The variance components obtained via ML are biased when the samples are small while REML estimates are unbiased. The problem with REML for model building is that the "likelihoods" obtained for models with different fixed effects are not comparable. Hence it is not valid to compare models with different fixed effects using a likelihood ratio test or AIC when REML is used to estimate the model. For this reason we have not used REML in this course. You must be aware of the distinction between ML and REML because REML is the default for most software packages. Thus you will generally need to explicitly specify maximum likelihood estimation if that's what you desire.)

2. Decide in advance whether to model the effect of treatment on patterns of change by

   (a) time by treatment interaction with time coded as a categorical variable,

   (b) time by treatment interaction with time coded as a continuous variable, or

(c) a treatment main effect ANCOVA model with baseline treated as a covariate and time treated as a categorical variable

The ML log likelihood (PROC MIXED METHOD=ML) may be used to compare any nested models differing by more than one degree of freedom.

3. Determine the final form of the regression (mean) model

4. Fit the final model using REML

5. Only estimation and test of covariate effects are considered here. It is also of great interest in testing and estimating covariance matrix.