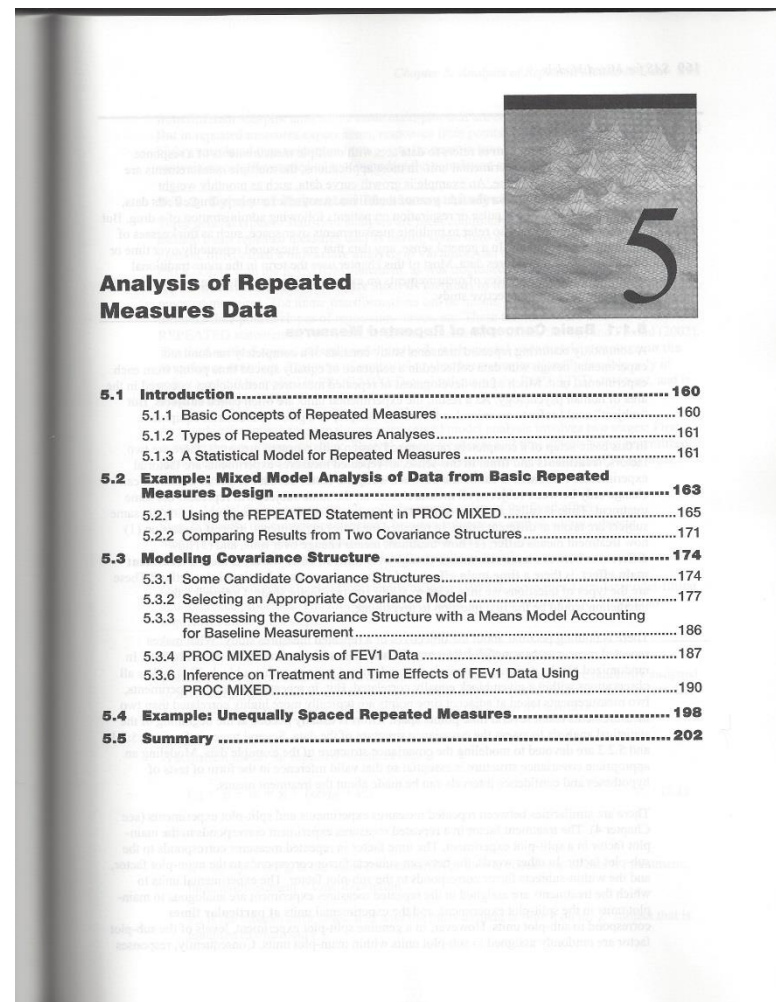
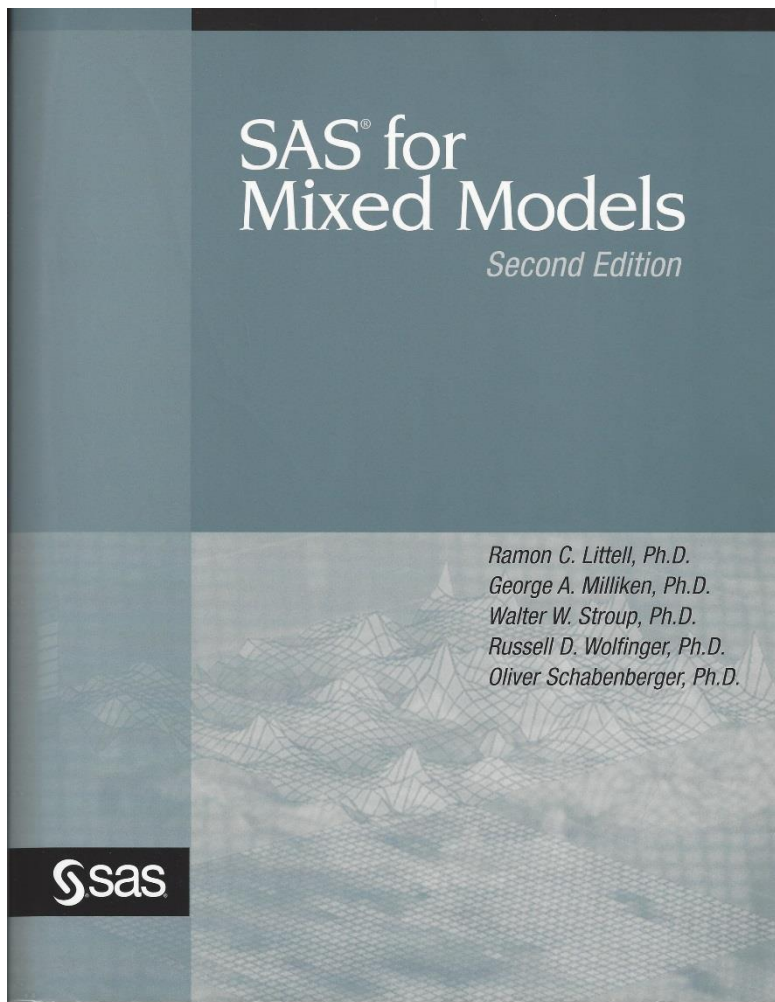




# **FITTING REPEATED MEASURES WITH JMP PRO 13: BIGGER AND BETTER**

**D. MCCORMACK – JMP TECHNICAL ENABLEMENT TEAM**





- Comparison of 3 asthma drug treatments: A (standard), C (test), P (placebo).
- Data was collected on three sets of 24 patients (one set per treatment).
- For each subject, a baseline measurement was made prior to administration of the drug, then hourly for eight hours.
- Forced expiration volume over 1 second (FEV1) was the measured response.

Littell, R.C., Pendergast, & Natarajan, R. (2000). Modelling Covariance Structure in the Analysis of Repeated Measures Data. *Statistics in Medicine*, 19, 1793 – 1819. Retrieved from [http://www.stat.unm.edu/~bedrick/glm/Littell\\_StatMed.pdf](http://www.stat.unm.edu/~bedrick/glm/Littell_StatMed.pdf)

Littell, R.C., Milliken, G.A., Stroup, W.W., Wolfinger, R.D., & Schabenberger, O. (2006). *SAS for Mixed Models, Chapter 5: Analysis of Repeated Measures Data*. SAS Press, Cary, NC. Data can be found at <http://support.sas.com/downloads/package.htm?pid=1793#>

- What are repeated measures designs?
  - Multiple measurements are taken on the same subject over time.
  - The subjects don't have to be people or animal, though they often are
  - The time periods don't have to be equally spaced, though they, often are.
  - Longitudinal studies can be conducted using repeated measures designs.
- Introduced in JMP Pro 11, expanded in JMP Pro 13
  - Three new covariance structures have been added: Compound Symmetry, Toeplitz, and Antedependent.
  - Unequal variance option has been added to all covariance structures except AR(1) and Spatial.
  - Indicator parameterization has been added.

- Roadmap to Analysis
  - Organize the data
  - Graph the data and correlations
  - Build some models
  - Gather model comparison info (and pick a model)
  - (Check the assumptions)
  - Test hypotheses – Time permitting

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**FITTING REPEATED MEASURES DATA WITH JMP® PRO 13**



**ORGANIZE THE DATA**



	Patient	Drug	Baseline	Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6	Hour 7	Hour 8
1	201	A	2.46	2.68	2.76	2.5	2.3	2.14	2.4	2.33	2.2
2	201	C	2.3	3.41	3.48	3.41	3.49	3.33	3.2	3.07	3.15
3	201	P	2.14	2.36	2.36	2.28	2.35	2.31	2.62	2.12	2.42
4	202	A	3.5	3.95	3.65	2.93	2.53	3.04	3.37	3.14	2.62
5	202	C	2.91	3.92	4.02	4.04	3.64	3.29	3.1	2.7	2.69
6	202	P	3.37	3.03	3.02	3.19	2.98	3.01	2.75	2.7	2.84
7	203	A	1.96	2.28	2.34	2.29	2.43	2.06	2.18	2.28	2.29
8	203	C	2.08	2.52	2.44	2.27	2.23	2.01	2.26	2.34	2.44
9	203	P	1.88	1.99	1.62	1.65	1.68	1.65	1.85	1.96	1.3
10	204	A	3.44	4.08	3.87	3.79	3.3	3.8	3.24	2.98	2.91
11	204	C	3.02	4.43	4.3	4.08	4.01	3.62	3.23	2.46	2.97
12	204	P	3.1	3.24	3.37	3.54	3.31	2.81	3.58	3.76	3.05
13	205	A	2.8	4.09	3.9	3.54	3.35	3.15	3.23	3.46	3.27
14	205	C	3.26	4.55	4.58	4.44	4.04	4.33	3.87	3.75	3.81
15	205	P	2.91	3.35	3.92	3.69	3.97	3.94	3.63	2.92	3.31
16	206	A	2.36	3.79	3.97	3.78	3.69	3.31	2.83	2.72	3
17	206	C	2.29	4.25	4.37	4.1	4.2	3.84	3.43	3.79	3.74
18	206	P	2.29	3.04	3.28	3.17	2.99	3.31	3.21	2.98	2.82
19	207	A	1.77	3.82	3.44	3.46	3.02	2.98	3.1	2.79	2.88
20	207	C	1.96	3	2.8	2.59	2.42	1.61	1.83	1.21	1.5
21	207	P	2.2	2.46	3.22	2.65	3.02	2.25	1.5	2.37	1.94
22	208	A	2.64	3.67	3.47	3.19	2.19	2.85	2.68	2.6	2.73
23	208	C	2.7	4.06	3.98	4.06	3.93	3.61	2.91	2.07	2.67
24	208	P	2.7	2.85	2.81	2.96	2.69	2.18	1.91	2.21	1.71
25	209	A	2.3	4.12	3.71	3.57	3.49	3.64	3.38	2.28	3.72
26											

- The hour columns need to be stacked.
- Create a second time variable with time as continuous.
- Subject values must be uniquely identified as Patient(Drug)

The screenshot shows the JMP Pro interface for a mixed model fit. The main window displays a data table with the following columns: Patient, Drug, Patient in Drug, Time Period, Time Period 2, Baseline, and FEV. The data is organized into rows, with the first 6 rows representing Patient 201 and the next 14 rows representing Patient 202. The FEV values range from 1.96 to 3.95.

Patient	Drug	Patient in Drug	Time Period	Time Period 2	Baseline	FEV	
1	201	A	201A	Hour 1	1	2.46	2.68
2	201	A	201A	Hour 2	2	2.46	2.76
3	201	A	201A	Hour 3	3	2.46	2.5
4	201	A	201A	Hour 4	4	2.46	2.3
5	201	A	201A	Hour 5	5	2.46	2.14
6	201	A	201A	Hour 6	6	2.46	2.4
7	201	A	201A	Hour 7	7	2.46	2.33
8	201	A	201A	Hour 8	8	2.46	2.2
9	202	A	202A	Hour 1	1	3.5	3.95
10	202	A	202A	Hour 2	2	3.5	3.65
11	202	A	202A	Hour 3	3	3.5	2.93
12	202	A	202A	Hour 4	4	3.5	2.53
13	202	A	202A	Hour 5	5	3.5	3.04
14	202	A	202A	Hour 6	6	3.5	3.37
15	202	A	202A	Hour 7	7	3.5	3.14
16	202	A	202A	Hour 8	8	3.5	2.62
17	203	A	203A	Hour 1	1	1.96	2.28
18	203	A	203A	Hour 2	2	1.96	2.34
19	203	A	203A	Hour 3	3	1.96	2.29
20	203	A	203A	Hour 4	4	1.96	2.43
21							

The left sidebar shows the project structure with the following items:

- FEV Data for Mixed Mod...
- FEV vs. Time Period
- Mean(FEV) vs. Time Period
- Fit Mixed - Unstructured
- Fit Mixed - Residual
- Fit Mixed - AR1
- Fit Mixed - Toeplitz
- Fit Mixed - Antedependen
- Fit Mixed - AR1 + CS
- Columns (7/0)
  - Patient
  - Drug
  - Patient in Drug
  - Time Period
  - Time Period 2
  - Baseline
  - FEV
- Rows
  - All rows: 576
  - Selected: 0
  - Excluded: 0
  - Hidden: 0
  - Labelled: 0

The status bar at the bottom indicates "evaluations done".



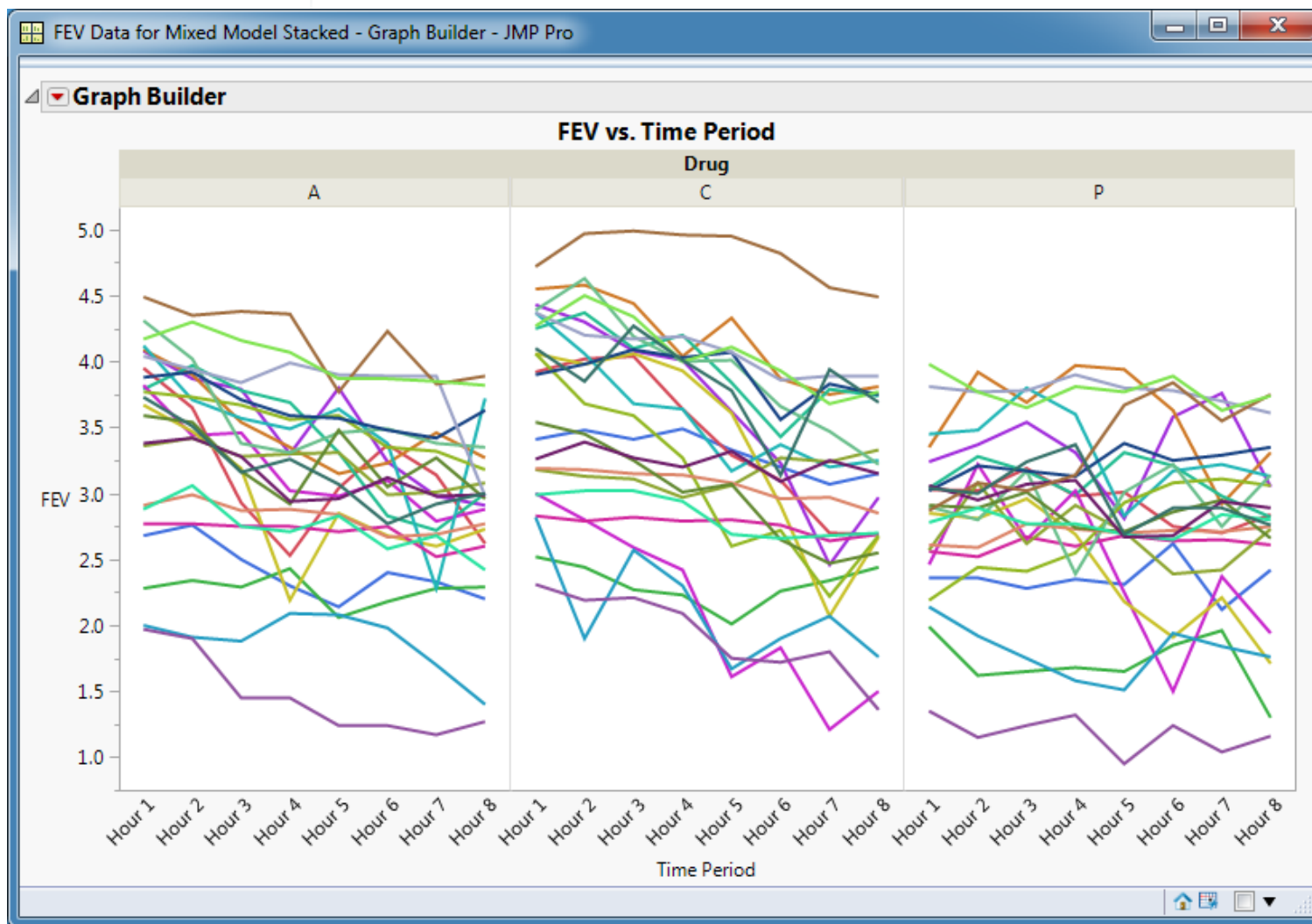
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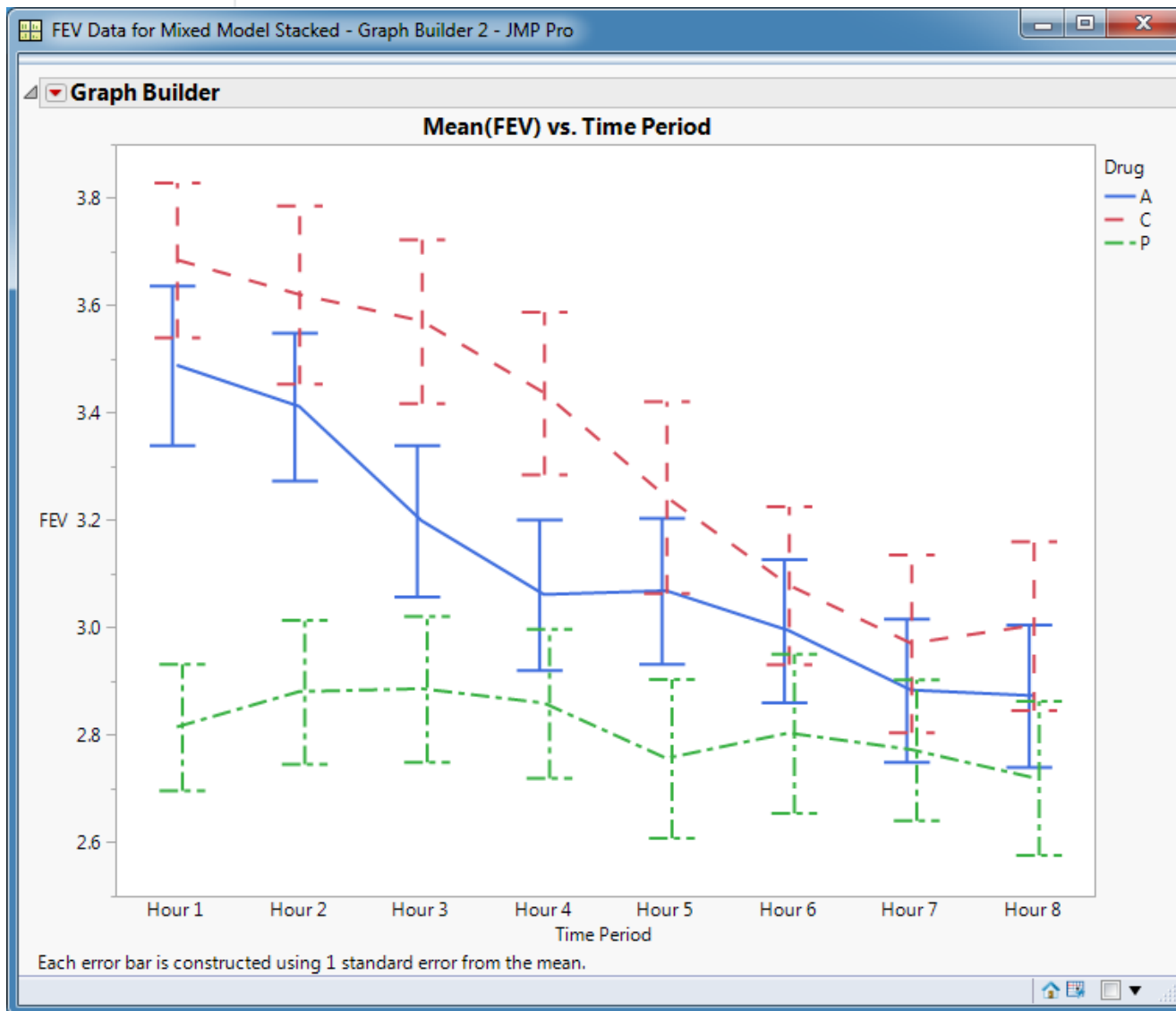
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**GRAPH THE DATA AND CORRELATIONS**

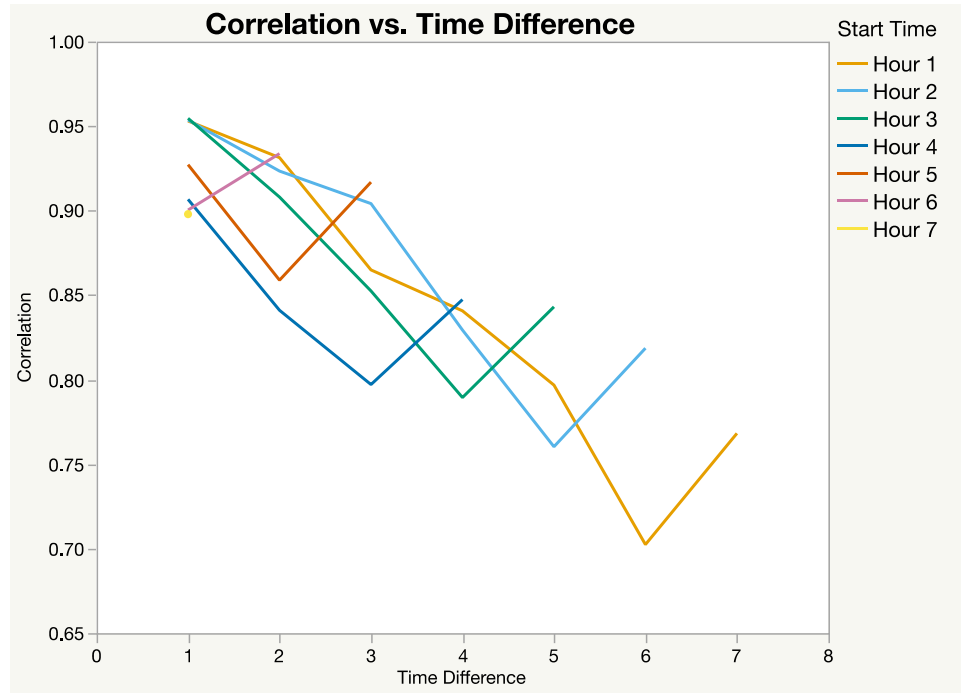
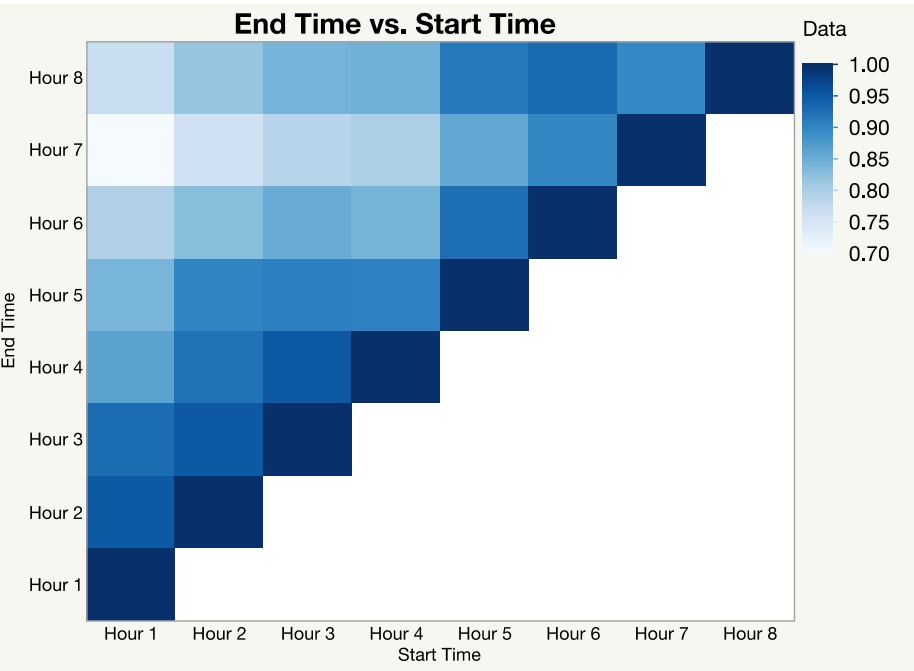






- Plot the stacked sample correlation table and note patterns.

	Hour 1	Hour 2	Hour 3	Hour 4	Hour 5	Hour 6	Hour 7	Hour 8
Hour 1	1.0000	0.9530	0.9313	0.8649	0.8407	0.7968	0.7024	0.7682
Hour 2	0.9530	1.0000	0.9536	0.9234	0.9041	0.8293	0.7603	0.8186
Hour 3	0.9313	0.9536	1.0000	0.9546	0.9080	0.8524	0.7894	0.8430
Hour 4	0.8649	0.9234	0.9546	1.0000	0.9066	0.8410	0.7971	0.8473
Hour 5	0.8407	0.9041	0.9080	0.9066	1.0000	0.9272	0.8588	0.9168
Hour 6	0.7968	0.8293	0.8524	0.8410	0.9272	1.0000	0.9003	0.9337
Hour 7	0.7024	0.7603	0.7894	0.7971	0.8588	0.9003	1.0000	0.8979
Hour 8	0.7682	0.8186	0.8430	0.8473	0.9168	0.9337	0.8979	1.0000



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**FITTING REPEATED MEASURES DATA WITH JMP® PRO 13**



**BUILD SOME MODELS**



$$\mathbf{Y} = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

$$\mathbf{e} \sim N(\mathbf{0}, \mathbf{R}) \quad \mathbf{u} \sim N(\mathbf{0}, \mathbf{G})$$

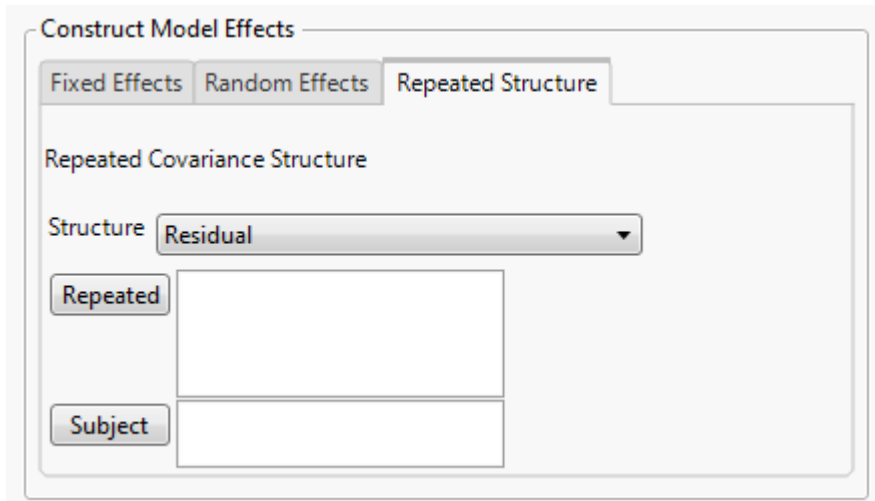
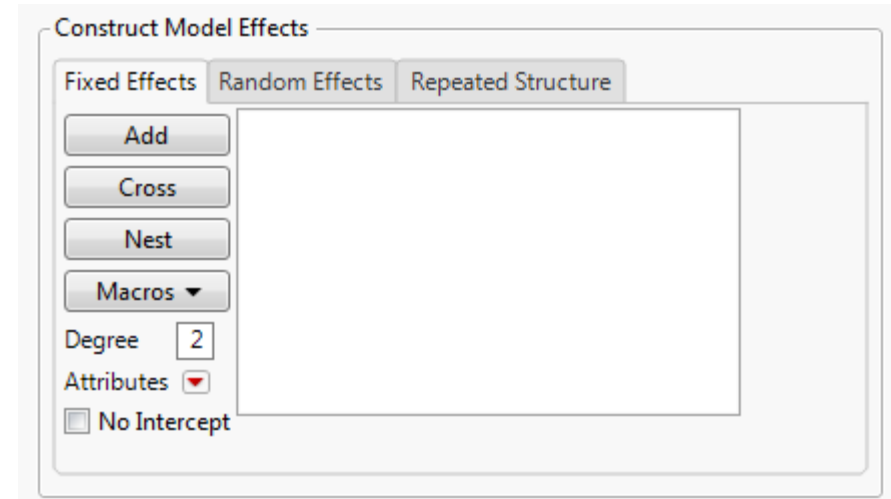
$$\text{Cov}(\mathbf{e}, \mathbf{u}) = \mathbf{0}$$

$$E(\mathbf{Y}|\mathbf{u}) = \mathbf{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} \quad \text{Var}(\mathbf{Y}|\mathbf{u}) = \mathbf{R}$$

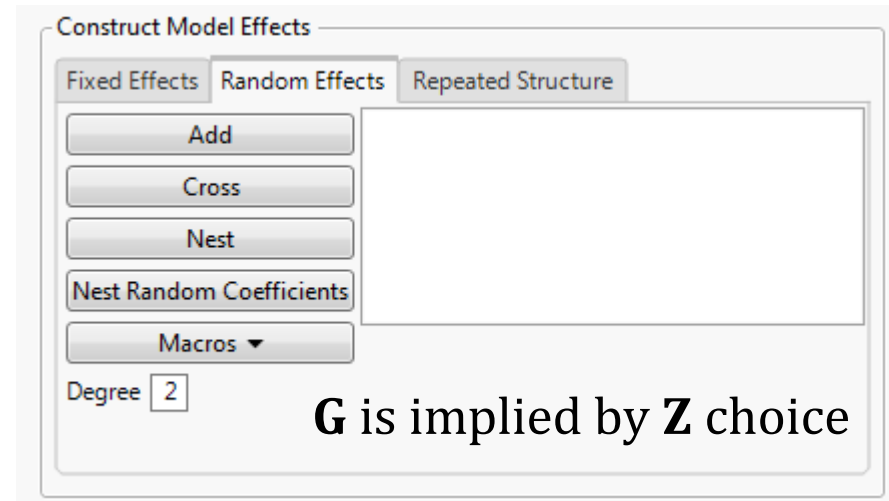
$$E(\mathbf{Y}) = \mathbf{X}\boldsymbol{\beta} \quad \text{Var}(\mathbf{Y}) = \mathbf{Z}\mathbf{G}\mathbf{Z}' + \mathbf{R}$$

$$FEV1_{ijk} = d_i + p_{jk} + t_k + dt_{ik} + f_{0j} + e_{jk}$$

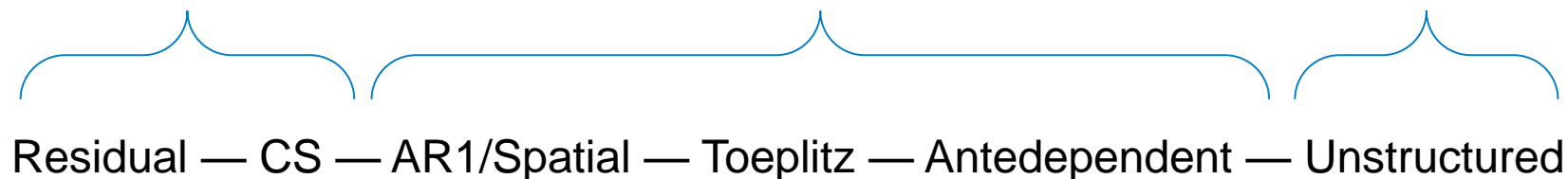
$$Y = X\beta + Zu + e \longrightarrow$$



$$e \sim N(0, \mathbf{R})$$



$$Y = X\beta + Zu + e$$



Less Structure/More Parameters 

 Fewer Parameters/More Assumptions



Construct Model Effects

Fixed Effects Random Effects Repeated Structure

Repeated Covariance Structure

Structure Residual

Repeated

Subject

Residual

Construct Model Effects

Fixed Effects Random Effects Repeated Structure

Repeated Covariance Structure

Structure Unequal Variances

Repeated Time Period  
*optional*

Subject *optional*

Unequal Variance

Construct Model Effects

Fixed Effects Random Effects Repeated Structure

Repeated Covariance Structure

Structure AR(1)

Repeated Time Period 2

Subject Patient  
Drug

Time Continuous

AR(1) and all Spatial

Construct Model Effects

Fixed Effects Random Effects Repeated Structure

Repeated Covariance Structure

Structure Compound Symmetry

Repeated Time Period

Subject Patient  
Drug

Time Categorical

Everything Else

**JMP Here!**



**GATHER MODEL COMPARISON INFO**



The screenshot shows a window titled "X - JMP Pro" containing a table with the following data:

Model	-2LogLike	AICc	BIC	Random Parameters	Fixed Parameters	Total Parameters	Window
AR(1) + RE	151.393	210.362	329.364	3	25	28	FEV Data for Mixed Model Stacked - Fit Mixed 7
Random Coefficients	150.522	211.708	334.849	3	25	28	FEV Data for Mixed Model Stacked - Fit Mixed 8
Toeplitz (Equal Variances)	131.41	201.55	341.162	8	25	33	FEV Data for Mixed Model Stacked - Fit Mixed 5
AR(1)	180.402	237.162	352.017	2	25	27	FEV Data for Mixed Model Stacked - Fit Mixed 4
Antedependent (Equal Variances)	152.631	222.771	362.382	8	25	33	FEV Data for Mixed Model Stacked - Fit Mixed 6
Compound Symmetry (Equal Variances)	256.023	312.783	427.638	2	25	27	FEV Data for Mixed Model Stacked - Fit Mixed 2
Unstructured	48.1827	184.899	435.905	36	25	61	FEV Data for Mixed Model Stacked - Fit Mixed 3
Residual	848.495	903.052	1013.75	1	25	26	FEV Data for Mixed Model Stacked - Fit Mixed

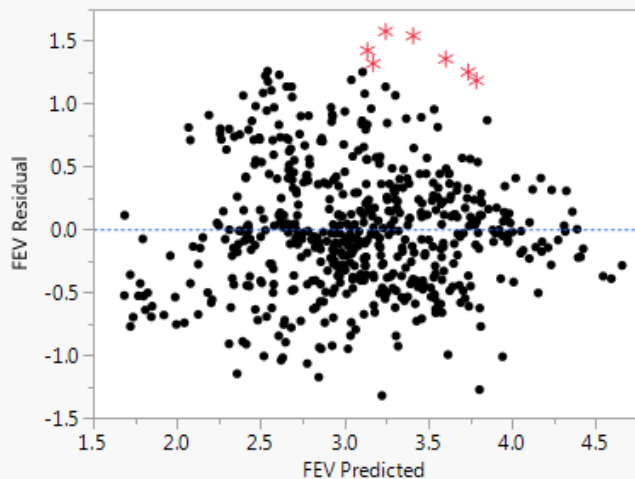


**CHECK THE ASSUMPTIONS**

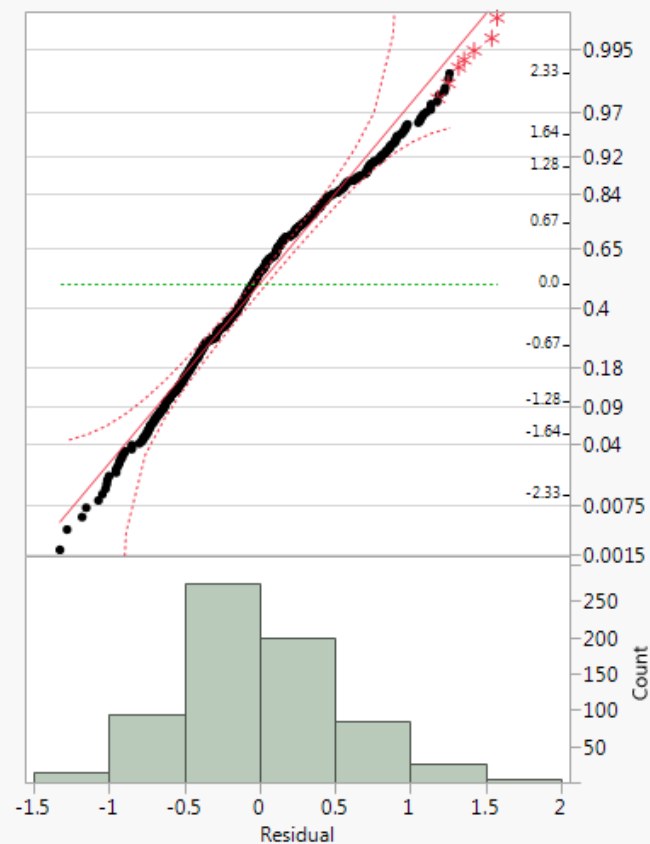


### Residual Plots

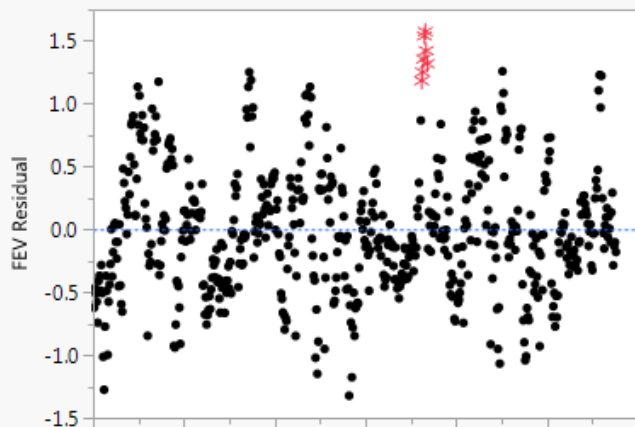
#### Residual by Predicted Plot

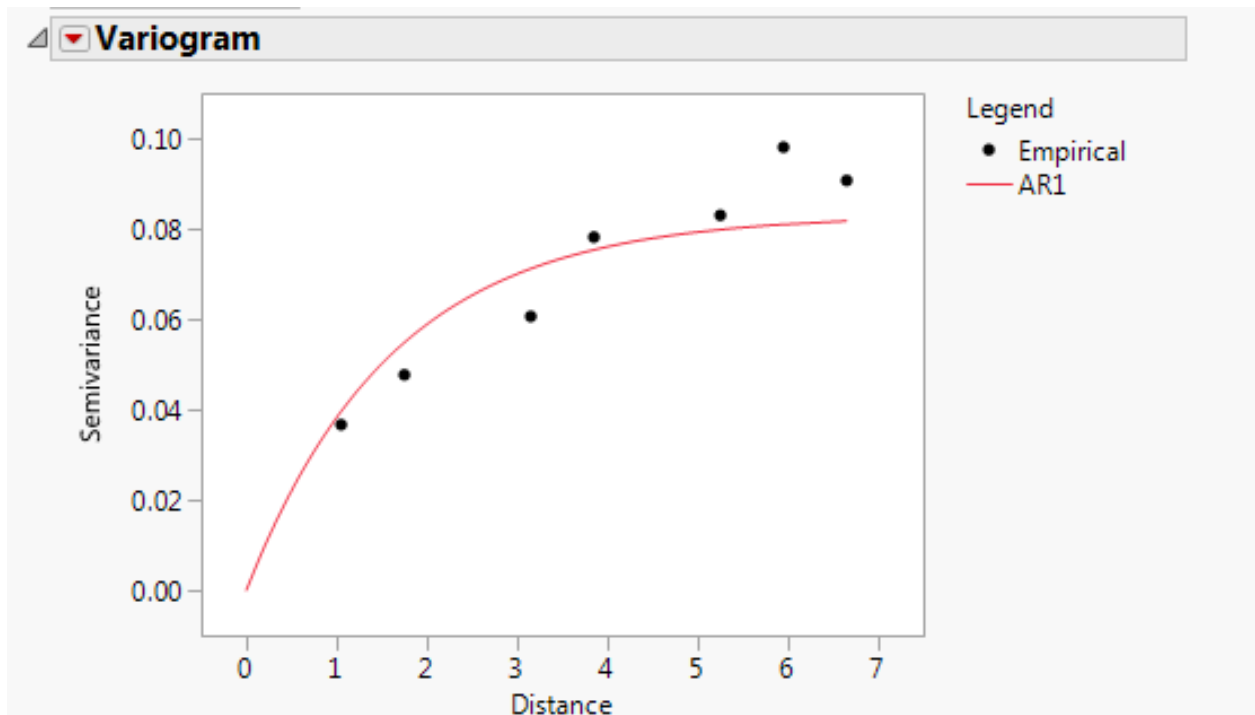


#### Residual Quantile Plot



#### Residual by Row Plot



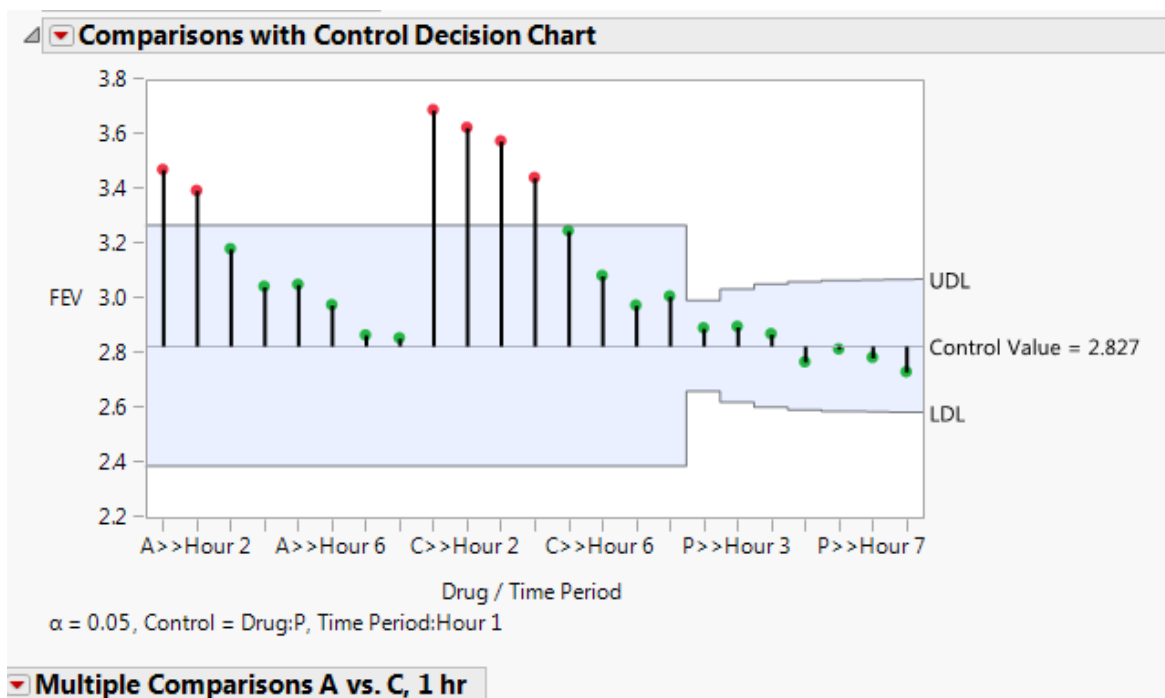
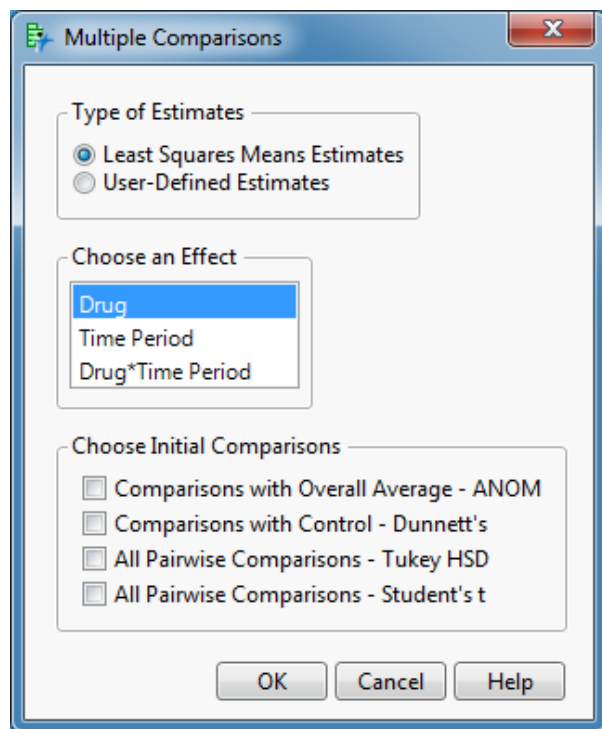




# TEST HYPOTHESES







Multiple Comparisons

Type of Estimates

Least Squares Means Estimates

User-Defined Estimates

Choose Drug levels

A  
C  
P

Choose Time Period levels

Hour 1  
Hour 2  
Hour 3  
Hour 4  
Hour 5  
Hour 6  
Hour 7  
Hour 8

Baseline

·  
·  
·  
·  
·  
·

Create user defined estimates by choosing factor settings and clicking the Add Estimates button as needed.

Add Estimates

Estimates for Comparison

Drug	Time Period	Baseline
A	Hour 1	2.6493056
C	Hour 1	2.6493056

Choose Initial Comparisons

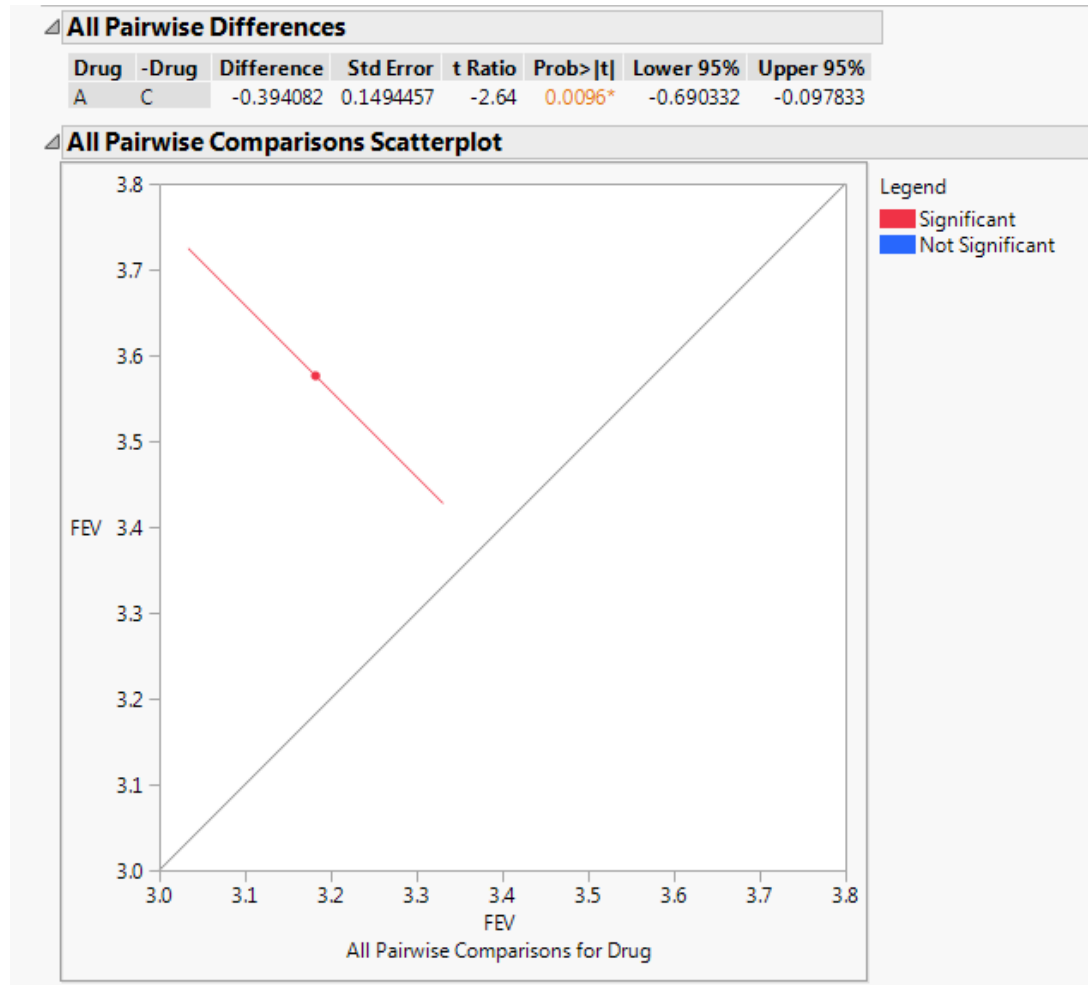
Comparisons with Overall Average - ANOM

Comparisons with Control - Dunnett's

All Pairwise Comparisons - Tukey HSD

All Pairwise Comparisons - Student's t

OK Cancel Help



# Extras

- Residual – Zero
- Compound Symmetry – Same correlation, regardless of time period.
  - Identical to a single random effect with the residual covariance structure.
- Unstructured – Anything goes
- AR(1) – Decreases at rate  $\rho$  each time period.
  - Example: if the variance at time 4 is  $\sigma^2$ , then the covariance between time four and seven is  $\rho^3\sigma^2$ .
- Spatial – Like AR(1) except decay rates differ depending on type.
  - Can be used with unequal time periods.
  - Spatial Power and AR(1) are the same.
  - Spatial anisotropic covariance structures require a second repeated variable to provided additional benefit. They are used to model correlation over (2-D) space.

- Toeplitz – covariance depends on number of periods away from the time zero variance.
  - Example: assuming equal variances, if the variance at time four is  $\sigma^2$ , the covariance between time four and seven is  $\rho_3\sigma^2$ . If the variances are unequal then the covariance is  $\rho_3\sigma_4\sigma_7$ .
- Antedependent – covariance depends on correlation associated with each time period from starting time to period of interest. Can be used with unequal time periods.
  - Example: with equal variances, if the variance at time 4 is  $\sigma^2$ , then the covariance between time four and seven is  $\rho_5\rho_6\rho_7\sigma^2$ . If the variances are unequal then the covariance is  $\rho_5\rho_6\rho_7\sigma_4\sigma_7$ .
- Random Coefficient – Correlation is captured by assuming time zero values and change over time each vary randomly around a given value for each subject. AKA random intercept/random slope models.

- Using the example above, the general form for MIXED is:

**PROC MIXED;**

```
CLASS drug patient hour;
```

```
MODEL fev1=drug hour drug*hour baseline / DDFM=KR;
```

```
REPEATED hour / options
```

```
RUN;
```

- Replace *options* with a value on the next page.
- For a random coefficient model, include the following statement:

```
RANDOM int hour2;
```

`hour2` has the same values as `hour`, except it is treated as continuous because it is not in the `CLASS` statement.

Structure	SAS Statement
Residual	No REPEATED statement
Unequal Variances	<code>SUBJECT = patient (drug)</code>
Compound Symmetry	<code>SUBJECT = patient (drug) TYPE=CS;</code>
CS – Unequal Variances	<code>SUBJECT = patient (drug) TYPE=CSH;</code>
AR(1)	<code>SUBJECT = patient (drug) TYPE=AR (1) ;</code>
Spatial Power	<code>SUBJECT = patient (drug) TYPE=SP (POW) (time2) ;</code>
Spatial with Nugget	<code>SUBJECT = patient (drug) TYPE=SP (POW) (time2) LOCAL;</code>
Toeplitz	<code>SUBJECT = patient (drug) TYPE=TOEP;</code>
Toeplitz Unequal Var	<code>SUBJECT = patient (drug) TYPE=TOEPH;</code>
Antedependent	<code>SUBJECT = patient (drug) TYPE=ANTE (1) ;</code>
Antedependent Equal Var	Not available
Unstructured	<code>REPEATED hour / SUBJECT = patient (drug) TYPE=UN;</code>

The other spatial structures, `SP (EXP)` , `SP (GAU)` , `SP (SPH)` , follow the same form.