Lecture 8: Repeated Measures Analysis

For JMP-IN commands see the JMP-IN manual page 329-338.

Repeated measures analysis is a broad area pertaining to methods used to analyze data where each observational unit has several recorded responses, typically over time. A variety of statistical methods may be relevant, depending on the assumed dependence between observations. A simple one-way ANOVA with repeated measures is described below.

Example: Thirty women were involved in a study to examine the effects of two drugs (A, B) on heart rates. The women were randomly divided into three groups of 10, with 10 receiving A and 10 receiving B. The remaining 10 were given a placebo. Four measurements were taken on each individual: a baseline heart rate two minutes after injecting the drug, and their heart rates after each of three subsequent five minute intervals. The data are given below.

Drug	Time: 1	2	3	4	Drug	Time: 1	2	3	4	Drug	Time: 1	2	3	4
p	80	77	73	69	p	64	66	68	71	p	75	73	73	69
p	72	70	74	73	p	74	74	71	67	p	71	71	72	70
p	76	78	74	71	p	73	68	64	64	p	76	73	74	76
p	77	78	77	73										
a	81	81	82	82	a	82	83	80	81	a	81	77	80	80
a	84	86	85	85	a	88	90	88	86	a	83	82	86	85
a	85	83	87	86	a	81	85	86	85	a	87	89	87	82
a	77	75	73	77										
b	76	83	85	79	b	75	81	85	73	b	75	82	80	77
b	68	73	72	69	b	78	87	86	77	b	81	85	81	74
b	67	73	75	66	b	68	73	73	66	b	68	75	79	69
b	73	78	80	70										

The analysis of these data would be straightforward if either a single drug or a single time period were considered. In particular, we would conduct a randomized block analysis of a single drug, treating times as treatments and persons as blocks. If only a single time period were considered, we would conduct a one-way ANOVA comparing drugs.

The repeated measures design for this experiment combines features of a randomized block experiment with a one-factor design, and is typically described as a one-factor experiment with repeated measures.

A Skeleton Analysis of the Repeated Measures Design

The basic model for the repeated measures design, as applied to this experiment is that the

$$\text{HeartRate} = \text{Grand Mean} + \text{Drug Effect} + \text{Person(Drug) Effect}$$
$$+\text{Time Effect} + \text{Drug} * \text{Time Interaction} + \text{Residual}.$$

The Person(Drug) Effect (read as: persons nested within drugs) is a nested random effect that measures the variability of the average response (averaged over time) of persons within the three groups.

As in previous analyses, the total variation in the data, as measured by the Total SS, is decomposed into a Model SS and a Residual or Error SS. The Model SS is then decomposed into SS for each of the effects in the model: drug, person(drug), time and time-by-drug interaction. A skeleton ANOVA table is given below.

Source	df	SS	MS
Drug	3-1=2		
Person(Drug)	9+9+9=27		
Time	4-1=3		
Drug*Time Interaction	$2 * 3 = 6$		
Error	81		
Total	120-1=119		

There are three usual tests of interest.

1. The test of no drug effect, which is based on the p-value for the $F-$statistic: F_{obs} = MS Dose/MS Person(Drug). Note that this test uses MS Person(Drug) in the denominator. In words, this is the F-test for no differences in a one-way ANOVA comparing drugs using the average heart rates over time as the response. This hypothesis is rejected when the mean heart rates, averaged over time, vary significantly across drugs relative to the variation within drug groups.

2. The test of no time effect, which is based on the p-value for the $F-$statistic: F_{obs} = MS Time/MS Error. This hypothesis is rejected when the marginal means for time (averaged across persons and drugs) vary significantly relative to the within sample variation.

3. The test of no interaction between drug and time is based on the p-value for the $F-$statistic: F_{obs} = MS Interaction/MS Error.

The analysis assumes that the correlation between time periods is identical for each pair of times. A more complex analysis is needed when this assumption fails.

Data Analysis

The **JMP-IN** output in the accompanying Word document gives an analysis of these data. Four variables are needed to uniquely represent each response in the spreadsheet: Drug (p,a, and b; nominal), Time (t1-t4; nominal), Person (1-10 in each group; nominal), and the Heart Rate (Rate; continuous). The data, as it appears in the spreadsheet, are given at the end of the **JMP-IN** output.

The **JMP-IN** implementation of the repeated measures analysis is carried out in the **FIT MODEL** platform window. Specify Rate as the response variable, and effects for Drug, Time, a Time by Drug interaction, and a **nested random** effect: Person(Drug). If the Person(Drug) effect is not defined to be random, then the F-test for no drug effects will incorrectly use the MS Error as the denominator in the F-test. Kyle will show you how to do this in Lab on Thursday.

The ANOVA table gives a p-value for testing whether there are any significant effects in the model. The p-value of $< .0001$ strongly suggests that that one or more of the effects (i.e. Drug, Time, Drug*Time, Person(Drug)), are important for explaining the variation in heart rates. The Effect Test Summary gives a breakdown of the Model SS and Model df into the SS and df for Drug, Time, the Drug by Time interaction and the Person(Drug) effect. The F-statistics and p-values for testing these effects are given. The p-values indicate that the Drug and Time effects are significant at the .01 level, and that there is a significant interaction between Drug and Time. Although there is an F-test for no Person(Drug) effect given in the table, it is of less interest than the other tests.

Let **us** interpret the LS Means, the profile plots, and the Tukey comparisons to elaborate on the conclusions that can be reached from these data.

In **Stata** we obtain similar, but *not exactly the same* output as JMP-IN via the command `anova rate drug / person|drug time drug*time, rep(time)`. We obtain the following output. You should verify that although the sums of squares are different for some of the effects, the p-values are the same as in the JMP-IN output:

```
                   Number of obs =     120     R-squared     =  0.9227
                   Root MSE      = 2.18249     Adj R-squared =  0.8865
      Source |  Partial SS    df       MS           F     Prob > F
-------------+----------------------------------------------------
       Model |  4606.76667    38  121.230702      25.45     0.0000
             |
        drug |  2438.46667     2  1219.23333      20.25     0.0000
person|drug |    1625.875    27  60.2175926
-------------+----------------------------------------------------
        time |  222.291667     3  74.0972222      15.56     0.0000
   drug*time |  320.133333     6  53.3555556      11.20     0.0000
             |
    Residual |     385.825    81   4.7632716
-------------+----------------------------------------------------
       Total |  4992.59167   119  41.9545518
```

It doesn't hurt to write down the model in abstract terms:

$$Y_{ijk} = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij} + \rho_{k(i)} + \epsilon_{ijk},$$

where Y_{ijk} is the heart rate of the k^{th} person to receive drug i at time j, μ is an overall *grand* mean, α_i is effect of drug i, $i = 1, 2, 3$, β_j is the effect of time j, $j = 1, 2, 3, 4$, $\rho_{k(i)}$ is the *random effect* associated with the k^{th} person, $k = 1, 2, \ldots, 10$, that received each of the 3 drugs, and ϵ_{ijk} is unexplained variability.

Note that the total variability as measured by the SS Total is equal to the sum: SS Total = SS drug + SS person|drug + SS time + SS drug*time + SS Residual. The SS Model is equal to the sum of all of the aforementioned terms except SS Residual. As usual, it is possible to get pairwise differences using `lincom`. For example, if there is no drug by time interaction, we might be interested in the differences in drug effects $\alpha_2 - \alpha_1$, $\alpha_3 - \alpha_1$, and $\alpha_3 - \alpha_2$. Therefore we could look at `lincom _b[drug[2]]-_b[drug[1]]`, et cetera. Finally, we obtain residuals, predicted values, et cetera, and perform diagnostics as in any other analysis.