Repeated Measures Designs

The time trend of individual responses to treatment is an important aspect of many experiments. Examples include experiments in which animals are weighed weekly to monitor growth under different nutrient conditions or field plots of perennial crops such as alfalfa are harvested several times in succession. **Repeated measures** occur frequently in clinical trials when patients are measured at regular intervals to monitor the response to medical treatment.

Repeated measures on each experimental unit provide information on the time trend of the response variable under different treatment conditions. Time trends can reveal how quickly the units respond to treatment or how long the treatment effects are manifest on the units of the study. Differences in trends among the treatments also can be evaluated.

Increased Precision with Repeated Observations

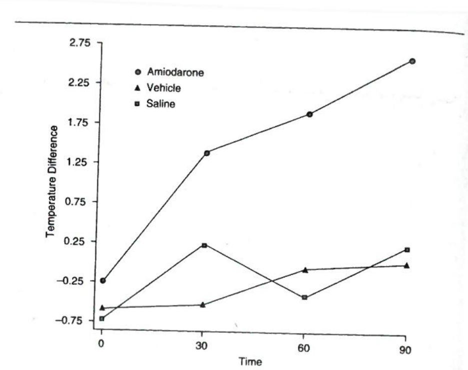
Repeated observations on the same experimental unit over time are often a more efficient use of resources than the use of a different experimental unit for each observation time. Not only are fewer units required, thereby reducing costs, but the estimation of time trends will be more precise. The increased precision results because measurements on the same unit tend to be less variable than measurements on different units. Thus, the effect of repeated measures is similar to the effect of blocking.

Example **Early Detection of Phlebitis in Amiodarone Therapy**

Treatment Design: Phlebitis is an inflammation of a vein that occurs upon intravenous administration of drugs. Three intravenous treatments were administered to test animals. They were (1) Amiodarone with a vehicle solution to carry the drug, (2) the vehicle solution only and (3) a saline solution.

Experiment Design: Rabbits, used as the test animals, were randomly assigned to the three treatment groups in a completely randomized design. A treatment solution was administered to the rabbit through an intravenous needle inserted in a vein of one ear. The temperature of both ears was monitored for several hours. An increase in the temperature of the treated ear was considered a possible early indicator of phlebitis. The difference in the temperatures of the two ears (treated minus untreated) was used as the response variable.

Repeated Measurements: The temperatures were observed every 30 minutes in each of the rabbits for the duration of the study. For the sake of illustration, the observations made at 0, 30, 60 and 90 minutes on five rabbits are shown.



```
# Handout #16

xmat <- c(1, -0.3, -0.2, 1.2, 3.1,
1, -0.5,  2.2, 3.3,   3.7,
1, -1.1,  2.4, 2.2,   2.7,
1,  1.0,  1.7, 2.1,   2.5,
1, -0.3,  0.8, 0.6,   0.9,
2, -1.1, -2.2, 0.2,   0.3,
2, -1.4, -0.2, -0.5, -0.1,
2, -0.1, -0.1, -0.5, -0.3,
2, -0.2,  0.1, -0.2,  0.4,
2, -0.1, -0.2,  0.7, -0.3,
3, -1.8,  0.2,  0.1,  0.6,
3, -0.5,  0.0,  1.0,  0.5,
3, -1.0, -0.3, -2.1,  0.6,
3,  0.4,  0.4, -0.7, -0.3,
3, -0.5,  0.9, -0.4, -0.3)

X <-matrix(data=xmat,ncol=5,byrow=TRUE)
Xmulti <- data.frame(trt=X[,1],time0=X[,2],time30=X[,3],time60=X[,4],time90=X[,5])

TimeLevels <- c(0,30,60,90)
TimeFactor <- as.factor(TimeLevels)
TimeFrame <- data.frame(TimeFactor)
TimeBind <- cbind(Xmulti$time0, Xmulti$time30, Xmulti$time60, Xmulti$time90)
TimeModel <- lm(TimeBind ~ factor(trt))

#
# Conduct a one-way repeated measures MANOVA
#

library(car)
rep.model <- Anova(TimeModel, idata=TimeFrame, idesign = ~ TimeFactor)
summary(rep.model)

# Output

Type II Repeated Measures MANOVA Tests:
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Term: (Intercept)

 Response transformation matrix:
       (Intercept)
time0            1
time30           1
time60           1
time90           1

Sum of squares and products for the hypothesis:
            (Intercept)
(Intercept)    24.06667

Sum of squares and products for error:
            (Intercept)
(Intercept)      43.764

Multivariate Tests: (Intercept)
                 Df test stat approx F num Df den Df   Pr(>F)
Pillai            1 0.3548051 6.599031      1     12 0.024597 *
Wilks             1 0.6451949 6.599031      1     12 0.024597 *
Hotelling-Lawley  1 0.5499193 6.599031      1     12 0.024597 *
Roy               1 0.5499193 6.599031      1     12 0.024597 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


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Term: factor(trt)

 Response transformation matrix:
       (Intercept)
time0            1
time30           1
time60           1
time90           1

Sum of squares and products for the hypothesis:
            (Intercept)
(Intercept)    141.5093

Sum of squares and products for error:
            (Intercept)
(Intercept)      43.764

Multivariate Tests: factor(trt)
                 Df test stat approx F num Df den Df     Pr(>F)
Pillai            2  0.763787 19.40079      2     12 0.00017371 ***
Wilks             2  0.236213 19.40079      2     12 0.00017371 ***
Hotelling-Lawley  2  3.233464 19.40079      2     12 0.00017371 ***
Roy               2  3.233464 19.40079      2     12 0.00017371 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


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Term: TimeFactor

 Response transformation matrix:
       TimeFactor1 TimeFactor2 TimeFactor3
time0            1           0           0
time30           0           1           0
time60           0           0           1
time90          -1          -1          -1

Sum of squares and products for the hypothesis:
            TimeFactor1 TimeFactor2 TimeFactor3
TimeFactor1    30.81667   12.183333   10.033333
TimeFactor2    12.18333    4.816667    3.966667
TimeFactor3    10.03333    3.966667    3.266667

Sum of squares and products for error:
            TimeFactor1 TimeFactor2 TimeFactor3
TimeFactor1      15.776       8.662       4.016
TimeFactor2       8.662      14.876       5.588
TimeFactor3       4.016       5.588       9.284

Multivariate Tests: TimeFactor
                 Df test stat approx F num Df den Df    Pr(>F)
Pillai            1 0.6763843 6.966951      3     10 0.0082072 **
Wilks             1 0.3236157 6.966951      3     10 0.0082072 **
Hotelling-Lawley  1 2.0900853 6.966951      3     10 0.0082072 **
Roy               1 2.0900853 6.966951      3     10 0.0082072 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


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```
Term: factor(trt):TimeFactor

 Response transformation matrix:
       TimeFactor1 TimeFactor2 TimeFactor3
time0            1           0           0
time30           0           1           0
time60           0           0           1
time90          -1          -1          -1

Sum of squares and products for the hypothesis:
            TimeFactor1 TimeFactor2 TimeFactor3
TimeFactor1   14.677333   6.1546667   2.8906667
TimeFactor2    6.154667   3.7373333   0.3253333
TimeFactor3    2.890667   0.3253333   1.2493333

Sum of squares and products for error:
            TimeFactor1 TimeFactor2 TimeFactor3
TimeFactor1      15.776       8.662       4.016
TimeFactor2       8.662      14.876       5.588
TimeFactor3       4.016       5.588       9.284

Multivariate Tests: factor(trt):TimeFactor
                 Df test stat approx F num Df den Df   Pr(>F)
Pillai            2 0.7247587 2.083879      6     22 0.096699 .
Wilks             2 0.3904482 2.001207      6     20 0.113354
Hotelling-Lawley  2 1.2660958 1.899144      6     18 0.136208
Roy               2 0.9581425 3.513189      3     11 0.052703 .
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


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Univariate Type II Repeated-Measures ANOVA Assuming Sphericity

                           SS num Df Error SS den Df       F    Pr(>F)
(Intercept)             6.017      1   10.941     12  6.5990 0.0245972 *
factor(trt)            35.377      2   10.941     12 19.4008 0.0001737 ***
TimeFactor             16.083      3   20.819     36  9.2704 0.0001117 ***
factor(trt):TimeFactor 10.063      6   20.819     36  2.9000 0.0207002 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1


Mauchly Tests for Sphericity

                       Test statistic p-value
TimeFactor                    0.85161 0.88653
factor(trt):TimeFactor        0.85161 0.88653


Greenhouse-Geisser and Huynh-Feldt Corrections
 for Departure from Sphericity

                        GG eps Pr(>F[GG])
TimeFactor             0.90727   0.000207 ***
factor(trt):TimeFactor 0.90727   0.025340 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

                        HF eps   Pr(>F[HF])
TimeFactor             1.19936 0.0001117035
factor(trt):TimeFactor 1.19936 0.0207001503
```