Stat 771, Fall 2011: Homework 3

Due Wednesday, March 23

The file `insulin.dat` contains longitudinal data from a study on $m = 36$ rabbits; 12 rabbits were randomly assigned to each of 3 groups: group 1 rabbits received the standard insulin mixture, group 2 rabbits received a mixture containing 1% less protamine than the standard, and group 3 rabbits received a mixture containing 5% less protamine. Rabbits were injected with the assigned mixture at time 0, and blood sugar measurements taken on each rabbit at the time of injection (time 0) and 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 hours post-injection. Each data record in the file `insulin.dat` represents a single observation; the columns of the data set are (1) rabbit number, (2) hours (time), (3) response (blood sugar level), and (4) insulin group (1, 2, or 3).

1. $\boxed{\text{Fit general model to get an idea of the covariance structure}}$ Recall from homework two that the estimated LOESS means are not quite linear from the spaghetti plots. Fit a model with the most general mean (completely unstructured) and an unstructured covariance matrix in each group, e.g.

```
proc mixed method=ml data=sugar;
 class rabbit hours group;
 model sugar=hours group hours*group / noint;
 repeated / subject=rabbit type=un group=group r=1,13,25 rcorr=1,13,25;
```

   Within each group, which (if any) of the available covariance matrices seem most plausible based on the fit? Do you think separate covariance matrices in each group is necessary?

2. $\boxed{\text{Choose a covariance matrix based on AIC}}$ Using completely unstructured means as in 1, fit 14 different models covering all covariance matrix assumptions discussed in class: `type=un`, `type=cs`, `type=csh`, `type=ar(1)`, `type=arh(1)`, `type=toep(2)`, `type=toeph(2)`; with both `group=group` included and not included. Prepare a table with the AIC and BIC for each of the 14 fits (these are given in the SAS output).

   (a) According to AIC which model is best?

   (b) According to BIC which model is best?

   (c) BIC penalizes more for adding parameters to a model when $N > 7$; is this happening here?

   (d) Using the models from (a) and (b), formally test whether each group should have it's own covariance matrix using a likelihood ratio test. State the null hypothesis, find the test statistic T_{LR}, the degrees of freedom df for χ^2_{df}, and report the $p-$value.

   (e) Is the covariance structure picked by AIC the same as the one you picked in part 1?

   Use the covariance picked by AIC for the rest of the analyses below.

3. $\boxed{\text{Keep the interaction?}}$

   (a) Obtain the estimated group means at each timepoint and plot them versus time. For example,

```
proc mixed method=ml data=sugar;
 class rabbit hours group;
 model sugar=hours group hours*group / noint outpm=out1;
 repeated / subject=rabbit type=ar(1) group=group; run;

ods listing gpath="c:/tim/stat771";
ods graphics on / reset=all imagename="mixed_rabbit_1";
proc sgplot data=out1(where=(rabbit=1 or rabbit=13 or rabbit=25));
title1 "Group Means";
 series x=hours y=pred / group=group; run;
ods graphics off;
```

   (b) Describe how the groups differ over time.

   (c) According to the Type 3 test in the SAS output, can we drop the `hours*group` interaction? Is this consistent with the Wald tests for the estimated *individual* `hours*group` effects in the table of coefficients?

   (d) Fit the model without the interaction, what happens to the AIC?

4. $\boxed{\text{When do differences occur?}}$ For the general model (with the interaction), formally test for pairwise differences in group means across the 7 time points. Let $g_i = 1, 2, 3$ indicate the group that rabbit i is in; g_i is in column 4 of the data. The model is

$$Y_{ij} = \tau_{g_i} + \gamma_j + (\tau\gamma)_{g_i j} + \epsilon_{ij},$$

where $\gamma_1, \ldots, \gamma_7$ are the time effects, τ_1, τ_2, τ_3 are the group effects, and $(\tau\gamma)_{ij}$ are the interaction terms. At 1.5 hours $j = 4$; the mean for group 2 minus the mean for group 1 at 1.5 hours is

$$\tau_2 + \gamma_4 + (\tau\gamma)_{24} - [\tau_1 + \gamma_4 + (\tau\gamma)_{14}] = \tau_2 - \tau_1 + (\tau\gamma)_{24} - (\tau\gamma)_{14}.$$

The first and second parts of this difference are given by

$$\begin{bmatrix} -1 & 1 & 0 \end{bmatrix} \begin{bmatrix} \tau_1 \\ \tau_2 \\ \tau_3 \end{bmatrix} = \tau_2 - \tau_1,$$

and

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} (\tau\gamma)_{11} \\ (\tau\gamma)_{21} \\ (\tau\gamma)_{31} \\ (\tau\gamma)_{12} \\ (\tau\gamma)_{22} \\ (\tau\gamma)_{32} \\ (\tau\gamma)_{13} \\ (\tau\gamma)_{23} \\ (\tau\gamma)_{33} \\ (\tau\gamma)_{14} \\ (\tau\gamma)_{24} \\ (\tau\gamma)_{34} \\ (\tau\gamma)_{15} \\ (\tau\gamma)_{25} \\ (\tau\gamma)_{35} \\ (\tau\gamma)_{16} \\ (\tau\gamma)_{26} \\ (\tau\gamma)_{36} \\ (\tau\gamma)_{17} \\ (\tau\gamma)_{27} \\ (\tau\gamma)_{37} \end{bmatrix} = (\tau\gamma)_{24} - (\tau\gamma)_{14}.$$

These two row vectors form part of an overall contrast vector to be fed to SAS. There are 21 hypothesis tests (7 times and 3 groups) total. For the first two time points my code looks like:

```
proc mixed method=ml data=sugar;
 class rabbit hours group;
 model sugar=hours group hours*group / noint solution chisq;
 repeated / subject=rabbit type=ar(1) group=group;
 estimate 'hr=0.0, grp2-grp1' group -1 1 0 hours*group -1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
 estimate 'hr=0.0, grp3-grp1' group -1 0 1 hours*group -1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
 estimate 'hr=0.0, grp3-grp2' group 0 -1 1 hours*group 0 -1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
 estimate 'hr=0.5, grp2-grp1' group -1 1 0 hours*group 0 0 0 -1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
 estimate 'hr=0.5, grp3-grp1' group -1 0 1 hours*group 0 0 0 -1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
 estimate 'hr=0.5, grp3-grp2' group 0 -1 1 hours*group 0 0 0 0 -1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0;
```

(a) We expect no differences at time zero; why is this? Do the pairwise hypothesis tests support this?

(b) At the 5% significance level, for which times is group 2 different from group 1? Summarize your findings in a coherent sentence that a doctor can understand.

(c) At the 5% significance level, for which times is group 3 different from group 1? Summarize your findings in a coherent sentence that a doctor can understand.

(d) Say we want to summarize differences halfway through (1.5 hours) and at the end (3.0 hours). Using a Bonferroni adjustment, summarize the results of the 6 pertinent hypothesis tests (simply multiply each of the 6 $p-$values by 6.

5. $\boxed{\text{Smoother, yet non-linear mean function?}}$ After presenting your analysis to the principal investigator (who funded the grant paying for the rabbit study), she lowers her glasses, sets down her coffee and says "This is interesting, but I wonder about having those trajectories smoother."

   (a) Fit a model where each group has its own quadratic mean, but *all three curves start at the same height at time zero.* This model is

   $$Y_{ij} = \beta_0 + \beta_1 t_j + \tau_{g_i} t_j + \beta_2 t_j^2 + \theta_{g_i} t_j^2 + \epsilon_{ij},$$

   where β_0 is the intercept, β_1 is the linear time effect, τ_1, τ_2, τ_3 are adjustments to the linear time effect for groups 1, 2, or 3, β_2 is the quadratic time effect, and $\theta_1, \theta_2, \theta_3$ are group adjustments to the quadratic effect. My code looks like

```
proc mixed method=ml data=sugar;
 class rabbit group;
 model sugar=hours hours*group hours*hours hours*hours*group / solution outpm=out2;
 repeated / subject=rabbit type=ar(1) group=group;
```

   (b) Perform a likelihood ratio test that this model is adequate versus the more general (unstructured mean with interaction) model fit in 4.

   (c) Obtain the fitted mean trajectories for each group as in 3 (the same code should work). Does the plot differ substantially? Which model would you use and why?

   (d) Obtain the same (Bonferroni-adjusted) hypothesis tests performed in 4(d). Are the $p-$values smaller, reflecting greater power obtained by fitting a simpler model? Are the six mean differences (3 pairwise differences at 1.5 hours and 3.0 hours) roughly the same from the two models?