BIO 226 Mid-Term Exam
April 8, 2014

Name:

Solutions

Department:

Instructions

1. There are three questions and you are asked to attempt all three questions.
2. Questions 1 is worth 40 points; Questions 2-3 are worth 30 points each.
3. Please show your work. We will give partial credit.

Question 1 (40 points). In a recent longitudinal clinical trial, 100 children with high levels of blood lead were randomized to receive treatment with either placebo (P) or succimer (S) (the latter is an orally administered chelating agent). Blood lead levels were recorded at baseline and at weeks 1, 4, and 6 on all children in the study. The investigators were primarily interested in determining whether treatment with succimer can reduce blood lead levels.

In the analysis of the data from this study, the response variable of main interest was the blood lead level (PbB). The measurement occasions were coded 0, 1, 4, and 6 with TIME=0 for measurements at baseline, TIME=1 for measurements at week 1, TIME=4 for measurements at week 4, and TIME=6 for week 6.

The investigators decided to subtract baseline measures from the three subsequent measures of blood lead levels. That is, they constructed three change scores, representing changes from baseline:

$$(PbB_1 - PbB_0), \quad (PbB_4 - PbB_0), \quad (PbB_6 - PbB_0)$$

and all analyses were conducted treating these three change scores as the responses.

The investigators noticed that the change score responses exhibited approximately linear trends over time in the two groups. Thus, Exhibit A gives partial model fitting information from fitting a linear trend model to the mean responses at the 3 repeated measures using restricted maximum likelihood (REML) with:

1. an unrestricted covariance matrix
2. a first-order autoregressive covariance with heterogeneous variances
3. a first-order autoregressive covariance with homogeneous variances
4. an exponential covariance
5. a compound symmetry covariance matrix
6. a mixed effects model with correlated random intercepts and slopes

a) 6 points, 1 for each model: For each of the six models above, indicate whether or not the model allows the covariances among pairs of repeated measures to vary according to how much time has elapsed between the recording of those measurements (You do **not** have to write out an expression for the covariance for each model).

1. **Unrestricted: Yes, there are no restrictions on the covariances, so covariances from different pairs of occasions are allowed to vary.**
2. **AR(1): Yes, AR(1) allows covariances to change as more time elapses between pairs of measurements.**
3. **ARH(1): Yes, ARH(1) allows covariances to change as more time elapses between pairs of measurements.**
4. **Exponential: Yes, the exponential model specifies the covariance between two repeated measurements to be an explicit function of time.**
5. **Compound Symmetry: No, this model forces all covariances to be the same.**
6. **Random intercepts and random slopes: Yes, this linear mixed model specifies the covariance between two repeated measurements to be an explicit function of the time elapsed between the recording of those measurements.**

b) 10 points: Using Exhibit A, construct a log likelihood ratio test to assess the adequacy of the exponential model. Is the exponential model defensible? Describe what features of the covariance or correlation matrix support your conclusion.

Covariance Model	# Parameters	-2 Res LL
Unrestricted	**6**	**1801.4**
Exponential	**2**	**1814.4**

Test H_0: Exponential model is defensible.

$$\textbf{LR stat} = 13, \textbf{on } 4 \textbf{ df } (p < .05)$$

Thus, we conclude that the exponential model for the covariance is not defensible for these data.

With an exponential correlation structure, we would expect:

1. **Equal variances. However, the unrestricted estimates of the variances range from 31.44 (baseline) to 35.63 (week 1).**
2. **Exponentialy decaying correlations. In particular, we would expect Corr$(1, 4)$ < Corr$(4, 6)$, since in the former case measurements are taken further apart. However, we find that** $r_{(1,4)} = 0.66 > r_{(4,6)} = 0.57$**.**

c) 14 points (minus 4 for no LRT comparing CS to UN, minus 4 for no AIC): Using Exhibit A, select one of the six models that provides a parsimonious, yet adequate, fit to the covariances. In your answer you should present results that support your choice of model.

Step 1: Compare the adequacy of the remaining four models to unrestricted covariance matrix (there is no need to compare the exponential model since it was not found to be defensible in part b)

Covariance Model	# Parameters	-2 Res LL	LR stat	df	p	AIC
Unrestricted	**6**	**1801.4**	**—**	**—**	**—**	**1813.4**
ARH(1)	**8**	**1806.9**	**5.5**	**2**	$p > .05$	**1814.9**
AR(1)	**4**	**1808.0**	**6.6**	**4**	$p > .10$	**1812.0**
CS	**2**	**1806.9**	**5.5**	**4**	$p > .20$	**1810.9**
Mixed Effects	**4**	**1804.8**	**3.4**	**2**	$p > .10$	**1812.8**

Conclusion: ARH(1), AR(1), CS, and Mixed Effects are all defensible.

Step 2: Compare the subsets of models that are nested in a standard way.

Covariance Model	# Parameters	-2 Res LL
ARH(1)	**4**	**1806.9**
AR(1)	**2**	**1808.0**

Test H_0: AR(1) model is defensible.

$$\textbf{LR stat} = 1.1\textbf{, 2 df } (p > .50)$$

Conclusion: Cannot reject H_0: AR(1) model is defensible.

Step 3: Compare AR(1), CS, and the mixed effects model. The first two are non-nested, and the last two are nested in a non-standard way. Make comparison in terms of AIC (smaller is better). Compound symmetry has the minimum AIC.

Final Conclusion: Select compound symmetry as the most parsimonous model that fits the data well.

d) 10 points: Suppose, instead of three responses per subject, investigators recorded weekly measurements for 10 consecutive weeks.

Name a likely disadvantage of the compound symmetry model for the covariance in this setting.

As the number of occasions increases, the assumptions of the compound symmetry model, namely equal variances for all time points and equal covariances for all pairs of observations recorded on the same subject, are less and less likely to hold. When this strict assumptions does not hold, the covariance model is misspecified, and there is potential for biased estimates of the standard errors.

Name a likely disadvantage of the unstructured model for the covariance in this setting.

The unstructured model is the least parsimonous, using $p(p+1)/2$ parameters in the model for the covariance structure. Thus, if we have $p = 10$ occasions, we will be estimating a large number of covariance parameters, which results in a loss of efficiency if a simpler model actually holds.

Question 2 (30 points). In a randomized placebo-controlled longitudinal clinical trial of 33 hemodialysis patients, 16 patients were treated with a new medication for pruritis (an itching sensation that triggers the desire to itch; a common symptom among hemodialysis patients) and 17 patients received placebo. Plasma histamine levels were recorded at baseline and at weeks 2,4,6 and 8. Note that there were some missing data. The investigators were interested in determining whether treatment with the new medication can reduce plasma histamine levels.

In the analysis of the data from this study, the response variable of interest was the plasma histamine level. The measurement occasions were coded 0, 2, 4, 6, 8, with TIME=0 for measurements at baseline, TIME=2 for measurements at week 2, TIME=4 for measurements at week 4, TIME=6 for measurements at week 6, and TIME=8 for measurements at week 8. Treatment group was coded as TRT=1 if randomized to the new medication and TRT=2 if randomized to the placebo.

The partial results of two analyses assuming an unstructured covariance are presented in Exhibit B. The displayed fit statistics are based on maximum likelihood (ML), whereas the displayed fixed effect estimates are from the restricted maximum likelihood (REML) fit. The investigators considered:

i. the saturated model (treating *TIME* as a categorical variable)

ii. the baseline or "constant effect" model. In this model, a new time variable, "POSTBASE", was constructed as follows:

$$\begin{aligned} \text{POSTBASE} &= 0 \text{ if baseline } (TIME = 0) \\ &= 1 \text{ if post-baseline } (TIME = 2, 4, 6, 8) \end{aligned}$$

a) 10 points: Using results in Exhibit B, choose the model for the mean that provides parsimonious, yet adequate, fit to the data. In your answer you should present results that support your choice of model.

Since the baseline-constant effects model is nested within the profile analysis, we conduct a likelihood ratio test to test whether the simpler model is adequate.

Mean Model	**# Parameters**	**-2 Res LL**
Saturated	**10**	**540.9**
Baseline	**4**	**548.5**

LR stat $= 7.6$**, 6 df** $(p > .20)$

We cannot reject H_0**, and conclude that the baseline or constant effect model is defensible.**

b) 10 points: Given your choice of model in part (a), give a detailed description of the effects of treatment on changes in plasma histamine levels.

Mean response at baseline (week 0) in the new medication group:

$$22.28 - 6.63 + 1.67 + 7.17 = 24.49$$

Mean response post-baseline (at weeks 2,4,6,8) in the new medication group:

$$22.28 - 6.63 = 15.65$$

Mean response at baseline (week 0) in the placebo group:

$$22.28 + 1.67 = 23.95$$

Mean response post-baseline (at weeks 2,4,6,8) in the placebo group:

$$22.28$$

The change from baseline in the new medication group is a decline of 8.839, while the change from baseline in the placebo group is a decline of 1.673. That is, there is a 7.166 unit greater decline (from baseline) in the new medication group when compared to the placebo group.

c) 10 points: Now suppose there are two baseline values for each person, so that now for six measurements per person, the POSTBASE values are 0, 0, 1, 1, 1, 1. Algebraically write out a mixed model that specifies that both the baseline mean and the postbase effect vary by subject, and that the averages of these subject-specific effects vary by treatment group. Please make sure you define all terms and assumptions of your model.

We write out a linear mixed effects model with fixed effects of trt, postbase, and trt*postbase, and subject-specific random intercepts and postbase effects. The model is

$$Y_{ij} = \beta_1 + \beta_2 Trt_i + \beta_3 Postbase_j + \beta_4 Trt_i * Postbase_j + b_{1i} + b_{2i} Postbase_j + \epsilon_{ij},$$

where

- Y_{ij} **is the histamine level for subject** i **at time** j**.**
- **If we define** $Trt_i = 1$ **if subject** i **was randomized to the new medication treatment arm, and 0 if a subject was randomized to placebo, then**

  β_1 **represents the mean histamine value at baseline in the placebo group**

  β_2 **represents the difference in mean histamine value at baseline between the new med and placebo groups,**

  β_3 **represents the difference in mean histamine value between post baseline and baseline in the placebo group,**

  β_4 **represents the difference in the post baseline effects between the new med and the placebo groups.**

We also assume:

$$\begin{pmatrix} b_{1i} \\ b_{2i} \end{pmatrix} \overset{iid}{\sim} N(\mathbf{0}, \mathbf{G})$$

$$\epsilon_{ij} \overset{iid}{\sim} N\left(0, \sigma^2\right),$$

with $\mathbf{b}_i$ **and** $\boldsymbol{\epsilon}_i$ **independent of one another,** $i = 1, \ldots, N$**.**

Question 3 (30 points). In a recent dental study, 27 children, 16 boys and 11 girls, were observed at 8, 10, 12, and 14 years of age. At each occasion, a measurement of the distance from the center of the pituitary to the pteryomaxillary fissure was made; there were no missing data. A primary objective of the study was to determine whether there is a difference between boys and girls with respect to growth in this dental measure.

In the analysis of these data, gender was coded as GENDER=F for female and GENDER=M for male. The measurement occasions were coded AGE=8, 10, 12, 14 for measurements taken at ages 8, 10, 12, and 14 respectively. Exhibit C gives partial model fitting information from fitting a random intercepts and random slopes model to the mean responses of the dental data using REML.

a) 12 points (4 + 4 + 4 for each of i, ii, iii): Using Exhibit C, provide an estimate of

i. the linear or constant rate of change over time in the mean response for females.

The mean (averaged over subjects) linear change over time for females is the fixed slope associated with this group:

0.78

ii. the linear or constant rate of change over time in the mean response for males.

The mean (averaged over subjects) linear change over time for males is the fixed slope associated with this group:

0.78 + 0.30 = 1.08

iii. the predicted linear change over time for child 1, who happens to be female.

The predicted linear change over time for subject 1 is the fixed slope associated with that subject's group plus her subject-specific random slope:

0.78 - 0.04 = 0.74.

b) 8 points (4 + 4 for each female and male): What is the estimated mean response at age 10 for females?

Note: The reference group for gender is females.

The estimated mean response at age 10 for females:

$$16.3406 + 0.7844 * 10 = 24.18$$

What is the estimated mean response at age 10 for males?

The estimated mean response at age 10 for males:

$$(16.3406 - 1.0321) + (0.7844 + 0.3048) * 10 = 26.20$$

c) 5 points: Using Exhibit C, give an expression (you don't have to simplify the final expression down to single numbers) for the range in which 95% of the linear rates of change in females fall.

This is

$$0.78 \pm 1.96 * \sqrt{0.03252},$$

where 0.78 is the estimated age coefficient and 0.03252 is the estimated variance for the random slopes.

d) 5 points: When there are missing data for some subjects, briefly explain why the random intercepts and slopes model is to be preferred over the two-stage approach that fits a regression model to each subject individually and performs an ANOVA or t-test on the resulting parameter estimates.

The two-stage model produces an estimated intercept and slope for each individual and then performs univariate analysis of these summary statistics. When some observations are missing, this approach does not take proper account of the variable amount of information provided by each subject, since each intercept and slope is weighted equally. The analysis based on the mixed model will employ an appropriate weighting automatically.

EXHIBIT A

1. Unrestricted Covariance Matrix

Estimated R Matrix for subject 1

Row	Col1	Col2	Col3
1	31.4358	22.0060	16.5048
2	22.0060	35.6317	19.9253
3	16.5048	19.9253	34.5005

Estimated R Correlation Matrix for subject 1

Row	Col1	Col2	Col3
1	1.0000	0.6575	0.5012
2	0.6575	1.0000	0.5683
3	0.5012	0.5683	1.0000

Fit Statistics

-2 Res Log Likelihood	1801.4
AIC (smaller is better)	1813.4
AICC (smaller is better)	1813.7
BIC (smaller is better)	1829.0

2. First-order Autoregressive Covariance with Heterogeneous Variances

Fit Statistics

-2 Res Log Likelihood	1806.9
AIC (smaller is better)	1814.9
AICC (smaller is better)	1815.0
BIC (smaller is better)	1825.3

3. First-order Autoregressive Covariance with Homogeneous Variances

Fit Statistics

-2 Res Log Likelihood	1808.0
AIC (smaller is better)	1812.0
AICC (smaller is better)	1812.1
BIC (smaller is better)	1817.3

4. Exponential Covariance

Fit Statistics

-2 Res Log Likelihood	1814.4
AIC (smaller is better)	1818.4
AICC (smaller is better)	1818.5
BIC (smaller is better)	1823.6

5. Compound Symmetric Covariance

Fit Statistics

-2 Res Log Likelihood	1806.9
AIC (smaller is better)	1810.9
AICC (smaller is better)	1810.9
BIC (smaller is better)	1816.1

6. Random Intercepts and Random Slopes Model

Fit Statistics

-2 Res Log Likelihood	1804.8
AIC (smaller is better)	1812.8
AICC (smaller is better)	1812.9
BIC (smaller is better)	1823.2

EXHIBIT B

i. Profile Analysis

Fit Statistics (ML)

-2 Log Likelihood	540.9
AIC (smaller is better)	570.9

Solution for Fixed Effects (REML)

Effect	time	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			22.2594	0.9536	31	23.34	<.0001
trt		1	-7.1800	1.3634	31	-5.27	<.0001
trt		2	0	.	.	.	.
time	0		1.7994	0.5525	31	3.26	0.0027
time	2		0.2759	0.4148	31	0.67	0.5109
time	4		0.3288	0.4104	31	0.82	0.4190
time	6		0.6586	0.3464	31	1.90	0.0666
time	8		0	.	.	.	.
time*group	0	1	7.7337	0.7829	31	9.88	<.0001
time*group	2	1	0.3322	0.5815	31	0.57	0.5719
time*group	4	1	0.0552	0.5641	31	0.10	0.9226
time*group	6	1	-0.5067	0.4818	31	-1.05	0.3011
time*group	8	2	0	.	.	.	.
time*group	2	2	0	.	.	.	.
time*group	2	2	0	.	.	.	.
time*group	4	2	0	.	.	.	.
time*group	6	2	0	.	.	.	.
time*group	8	2	0	.	.	.	.

Type 3 Tests of Fixed Effects (REML)

Effect	Num DF	Den DF	F Value	Pr > F
trt	1	31	22.32	<.0001
time	4	31	133.32	<.0001
trt*time	4	31	61.99	<.0001

ii. Baseline or “Constant Effects” Model

Fit Statistics (ML)

-2 Log Likelihood	548.5
AIC (smaller is better)	578.5

Solution for Fixed Effects (REML)

Effect	trt	postbase	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			22.2783	0.7846	31	28.40	<.0001
trt	1		-6.6252	1.1290	31	-5.87	<.0001
trt	2		0	.	.	.	.
postbase		0	1.6733	0.3223	31	5.19	<.0001
postbase		1	0	.	.	.	.
group*postbase	1	0	7.1665	0.4627	31	15.49	<.0001
group*postbase	1	1	0	.	.	.	.
group*postbase	2	0	0	.	.	.	.
group*postbase	2	1	0	.	.	.	.

EXHIBIT C

Estimated G Matrix

Row	Effect	child	Col1	Col2
1	Intercept	1	5.7864	-0.2896
2	age	1	-0.2896	0.03252

Estimated G Correlation Matrix

Row	Effect	child	Col1	Col2
1	Intercept	1	1.0000	-0.6676
2	age	1	-0.6676	1.0000

Solution for Fixed Effects

Effect	gender	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		16.3406	1.0185	25	16.04	<.0001
gender	M	-1.0321	1.5957	54	0.65	0.5205
gender	F	0	.	.	.	.
age		0.7844	0.08600	25	9.12	<.0001
age*gender	M	0.3048	0.1347	54	-2.26	0.0277
age*gender	F	0	.	.	.	.

Solution for Random Effects

Effect	child	Estimate	Std Err Pred	DF	t Value	Pr > |t|
Intercept	1	-0.6413	1.8112	54	-0.35	0.7247
age	1	-0.04475	0.1543	54	-0.29	0.7729
Intercept	2	-0.6602	1.8112	54	-0.36	0.7169
age	2	0.09029	0.1543	54	0.59	0.5608
Intercept	3	-0.2489	1.8112	54	-0.14	0.8912
age	3	0.1136	0.1543	54	0.74	0.4649
Intercept	4	1.6611	1.8112	54	0.92	0.3632
age	4	0.02821	0.1543	54	0.18	0.8556
Intercept	5	0.5710	1.8112	54	0.32	0.7538
age	5	-0.05496	0.1543	54	-0.36	0.7230

$\alpha = 0.05$ critical values for chi-squared distribution, for specific degrees of freedom (df)

df	Critical Value
1	3.84
2	5.99
3	7.81
4	9.49
5	11.07
6	12.59
7	14.06
8	15.50
9	16.92
10	18.31
11	19.68
12	21.03
13	22.36
14	23.68
15	25.00

Example use of table:

Consider the following two scenarios where you construct a likelihood ratio test (LRT) statistic.

(a) Suppose LRT = 4.55 with 3 df. Then, because $4.55 < 7.81$, we cannot reject the null hypothesis at the 5% significance level and $p > 0.05$.

(b) Suppose LRT = 20.55 with 5 df. Then, because $20.55 > 11.07$, we can reject the null hypothesis at the 5% significance level and $p < 0.05$.