BIO 226 Mid-Term Exam
April 7, 2015

Name:

Solutions

Department:

Instructions

1. There are four questions and you are asked to attempt all four questions.
2. You have 1 hour and 40 minutes for the test.
3. Questions 1-3 are worth 30 points; Question 4 is worth 10 points.
4. Please note there is a table of chi-squared critical values ($\alpha = 0.05$) on the last page of the test.
5. You must work alone but may use any class materials and books.

In a recent longitudinal clinical trial, 120 children with high levels of blood lead were randomized to receive one of three treatments: placebo, low dose succimer, or high dose succimer. Blood lead levels were recorded at baseline and at weeks 2, 4, and 6, and 8 on all children in the study. The investigators were primarily interested in determining whether treatment with succimer can reduce blood lead levels, and whether there might be differences in longitudinal trends between the low-dose to high-dose of treatment.

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 week=0, 2, 4, 6, and 8, with week=0 for measurements at baseline (pre-randomization), week=2 for measurements at week 2, week=4 for measurements at week 4, and so on. The groups are coded as trt=1 for placebo, trt=2 for low-dose succimer group, and trt=3 for high-dose succimer group.

PLEASE NOTE, THE DATA CONSIDERED HERE IS NOT FROM THE SAME STUDY AS USED IN CLASS LECTURES, SO DON'T ASSUME THE PATTERNS ARE AS WE FOUND THEM IN LECTURE

Question 1 (30 points). Exhibit A gives partial model fitting information from fitting a linear trend model to the mean responses at the 4 repeated measures using restricted maximum likelihood (REML) with:

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

a) Inspect the estimated covariance matrix from the unstructured covariance model. Describe two notable and important features of this matrix, and for each of these features, list which of the above covariance structures (2)-(4) are likely to accommodate that feature and which ones do not.

1. **The occasion-specific variance estimates vary with time, from 92.7 at time 1 down to 19.2 at time 4.**
2. **The correlations in general tend to decrease with increasing time separating a pair of measurements, although this is not true in all cases.**

Out of covariance structures 2-4,

1. **Only ARH(1) (model 2) allows variances to vary with measurement occasion.**
2. **ARH(1) and Exponential (models 2 and 3) allow correlations to change as the distance between measurement occasions increases.**

b) Consider a likelihood ratio test to assess whether the exponential model fits the data adequately, given the assumed mean model. Write out the null and alternative hypothesis corresponding to this test (Note you are not asked to perform this test until the next question).

H_0: The exponential covariance model is adequate for the observed data.

H_1: The exponential structure is inadequate, and unstructured covariance model is necessary.

c) Conduct the test outlined in (b). What do you conclude?

The likelihood ratio statistic testing the hypothesis given in (b) is LR $= 3207.5 - 3085.2 = 122.3$ **on df=15-2=13. With a critical value** $\chi^2_{13,.95} = 22.36$**, this is highly significant, suggesting that the exponential model is not adequate for these data when compared against the unstructured matrix.**

Point to a feature in the unstructured matrix estimates that supports this conclusion.

Under the exponential model, the variances along the diagonal should all be the same, but the unstructured estimates range from 92.7112 down to 19.1711.

d) Consider the output for the linear mixed model with random intercepts. Using the estimates from this output, write out the estimate of the variance covariance matrix (Σ) from this model fit.

$$\begin{bmatrix} \sigma_b^2 + \sigma^2 & \sigma_b^2 & \sigma_b^2 & \dots & \sigma_b^2 \\ \sigma_b^2 & \sigma_b^2 + \sigma^2 & \sigma_b^2 & \dots & \sigma_b^2 \\ \sigma_b^2 & \sigma_b^2 & \sigma_b^2 + \sigma^2 & \dots & \sigma_b^2 \\ . & . & . & \dots & . \\ . & . & . & \dots & . \\ \sigma_b^2 & \sigma_b^2 & \sigma_b^2 & \dots & \sigma_b^2 + \sigma^2 \end{bmatrix}$$

where $\widehat{\sigma}_b^2 = 24.1230$ **and** $\widehat{\sigma}^2 = 21.3109$

e) For these data, based on the output from the two mixed models, evaluate whether there is a need for random slopes. What does your evaluation tell you in terms of whether there is heterogeneity in subject-specific longitudinal changes over time?

The random intercepts model is nested within the random intercepts - random slopes model. However, this is an instance where the likelihood ratio statistic (defined as -2 * difference in the maximized likelihoods) is not asymptotically distributed as a chi-squared random variable with the number of df equal to the difference in the number of parameters between the two models. See the nice discussion of this in Lab 5. One work-around of this issue is to compare the AIC values, and select the model that yields the smallest AIC. The AIC is 3315.4 for the random intercept model and 3106.9 for the random intercepts and random slopes model. Therefore, we select the random intercepts and random slopes model as our final model, and conclude that there exists significant heterogeneity in the subject-specific longitudinal changes over time.

Question 2 (30 points). Exhibit B shows partial results from fitting four models to the same blood lead data, all assuming an unstructured covariance model. 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 four regression models are:

i. the means profile model

ii. the linear trend model

iii. the linear trend model minus the trt * week interactions

iv. the linear trend model minus the trt * week and the trt terms

a) For the mean profiles model (i), interpret each of

- the intercept
- the `trt 2` parameter
- the `week 6` parameter
- the `trt*week 3 6` parameter

The intercept represents the mean blood lead level for the placebo group at baseline

The `trt 2` parameter represents the difference in mean blood lead level between the low-dose group and the placebo group at baseline.

The `week 6` parameter represents the difference in mean blood lead level between week 6 and baseline in the placebo group.

The `trt*week 3 6` parameter represents the difference between the week 6 vs baseline difference in mean outcome for the high dose group as compared to that same difference in the placebo group.

b) For the mean profiles model, interpret the testing result for the trt x week interaction listed under "Test of the Fixed Effects". Name one reason why this test might not be optimal for this analysis.

The trt x week interaction listed in the Type 3 Tests of Fixed Effects is the Wald test of the null hypothesis that the temporal profiles across time are parallel in the three treatment groups, versus the alternative that at least one of the curves are not parallel to the others. This corresponds to the condition that the rates of change in mean blood lead levels is the same in the three groups, without specifying any functional form for these profiles.

If the trends can be captured with a simpler parametric curve model, this test based on mean profiles will not be as powerful as a parametric curve model and we will lose power to detect differences in temporal trends among groups.

c) Based on the mean profiles analysis (i), provide an estimate (no need to test) of how the longitudinal change between week 2 and week 8 differs between the low-dose and high-dose succimer groups.

The difference in mean response between week 8 and week 2 in the low-dose group is

$$(week8 + trt2 * week8) - (week2 + trt2 * week2) = (-2.8040 - 3.9920) - (-1.1359 + 0.3119)$$

The difference in mean response between week 8 and week 2 in the high-dose group is

$$(week8 + trt3 * week8) - (week2 + trt3 * week2) = (-2.8040 - 5.7414) - (-1.1359 - 0.9895)$$

The estimate of how this longitudinal change differs between the low-dose and high-dose groups is the difference of these two estimates.

d) Based on the linear trend model (ii), provide estimates of the change in the mean blood lead levels over time for each of the three treatment groups.

Placebo: $\beta_4 = -0.3367$

Low-Dose: $\beta_4 + \beta_5 = -0.3367 + (-0.4692)$

High-Dose: $\beta_4 + \beta_6 = -0.3367 + (-0.7072)$

e) Assuming the means follow a linear trend, conduct a likelihood ratio test of whether the mean blood lead levels from the different groups are parallel for the duration of the study. What do you conclude?

Based on model (ii), the test that the means are parallel corresponds to the condition that both the trt x time interactions are equal to zero. Therefore, we compare model (ii) and model (iii). The likelihood ratio statistic is $LR = 3090.1 - 3082.6 = 7.5$ **on** $df = 6 - 4 = 2$**. The statistic is greater than the cutoff** $\chi^2_{2,95} = 5.99$**. Thus, we reject the null hypothesis and, under the assumption that trends over time are linear, we find strong evidence that the three sets of means are not parallel.**

Question 3 (30 points). Again consider the same blood lead data as considered in Problems 1 and 2. Exhibit C presents results from a random intercepts and slopes model, assuming a linear parametric curve model for the population averaged mean.

a) Write out the random intercepts and slopes model that is being fit, making sure to write out the definition of all covariates and all assumptions (including those involving sampling) made by the model.

$$Y_{ij} = \beta_1 + \beta_2 trt2_i + \beta_3 trt3_i + \beta_4 week_j + \beta_5 trt2_i * week_j + \beta 6 trt3_i * week_j + b_{1i} + b_{2i} week_j + \epsilon_{ij}.$$

where

$trt2_i = 1$ **if subject** i **received low-dose and 0 otherwise,** $trt3_i = 1$ **if subject** i **received high-dose and 0 otherwise, and** $week_j = 0, 2, 4, 6,$ **or** 8**.**

$$\begin{pmatrix} b_{1i} \\ b_{2i} \end{pmatrix} \overset{iid}{\sim} N(\mathbf{0}, \mathbf{G}), \qquad \epsilon_i \overset{iid}{\sim} N\left(\mathbf{0}, \sigma^2 \mathbf{I}\right),$$

with the random effects and the residual errors independent.

We assume the subjects are randomly sampled and indepedent of one another.

b) What is the mean (across subjects) intercept for the low-dose succimer group?

This is the intercept plus the `trt 2` **effect:** $27.0347 + 0.2605$

c) What is the mean (across subjects) slope for the high-dose succimer group?

This is the week plus the `week*trt 3` **effect:** $-0.3187 - 0.6965$

d) Quantify how much the the subject-specific slopes in the high-dose succimer group vary around the mean value you provided in (c) by writing out an expression for the range of values in which 95% of all slopes from this group fall (You do not have to do the math and give the numerical values of the endpoints).

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$$-1.0152 \pm 1.96\sqrt{1.1440}$$

e) Suppose interest focuses on the prediction of subject-specific longitudinal changes in blood lead level over time. Based on the random intercepts and slopes model, write out the linear regression formula for subject 1, who received a high-dose of succimer treatment.

Using the notation from (a), the requested linear regression is

$$\begin{aligned} Y_{ij} &= (\beta_1 + \beta_3 + b_{11}) + (\beta_4 + \beta_6 + b_{21})\, week_j + \epsilon_{ij} \\ &= (27.0347 + 0.1220 + 2.9926) + (-0.3187 + -0.6965 + 2.2607)\, week_j + \epsilon_{ij}. \end{aligned}$$

Question 4 (10 points). For the blood lead study considered in Problem 2, your scientific collaborator expressed concern that the mean profile analysis contains too many parameters. He suggested that you either

- take differences between each post-baseline measurement and the baseline measurement for each subject, and then conduct a mean profile analysis on this difference vector

$$(Y_{i2} - Y_{i0}, Y_{i4} - Y_{i0}, , Y_{i6} - Y_{i0}, Y_{i8} - Y_{i0})$$

  of length four, which will reduce the number of parameters.

- run a model that treats the post-baseline tmeasurements as the response, and includes group (categorical placebo, low-dose, high-dose), week, group x week interaction, and each subjects baseline response as covariates.

For each of these two options, state whether that particular analysis strategy is valid for this particular study, and provide a brief justification for your answer.

Adjustment for baseline through analysis of covariance is generally recommended only for randomized studies. Since this study is randomized with baseline measures in each group presumably having the same distribution, this is an appropriate analysis strategy for this study.

Moreover, the model based on the differences will give the exact same inferences on the changes over time as the means profile analysis, and so is also valid in the case

EXHIBIT A

1. Unrestricted Covariance Matrix

Estimated R Matrix for id 1

Row	Col1	Col2	Col3	Col4	Col5
1	92.7112	67.2293	50.5826	25.7933	13.2260
2	67.2293	61.2930	39.7627	21.3018	8.0741
3	50.5826	39.7627	41.9338	16.3775	8.4960
4	25.7933	21.3018	16.3775	20.5887	9.1378
5	13.2260	8.0741	8.4960	9.1378	19.1711

Estimated R Correlation Matrix for id 1

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.8918	0.8112	0.5904	0.3137
2	0.8918	1.0000	0.7843	0.5996	0.2355
3	0.8112	0.7843	1.0000	0.5574	0.2996
4	0.5904	0.5996	0.5574	1.0000	0.4599
5	0.3137	0.2355	0.2996	0.4599	1.0000

Fit Statistics

-2 Res Log Likelihood	3085.2
AIC (smaller is better)	3115.2
AICC (smaller is better)	3116.1

2. First-order Autoregressive Covariance with Heterogeneous Variances

Fit Statistics

-2 Res Log Likelihood	3164.4
AIC (smaller is better)	3176.4
AICC (smaller is better)	3176.6
BIC (smaller is better)	3193.2

3. Exponential Covariance

Fit Statistics

-2 Res Log Likelihood	3207.5
AIC (smaller is better)	3211.5
AICC (smaller is better)	3211.5
BIC (smaller is better)	3217.0

4. Random Intercepts Model

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
Intercept	id	24.1230
Residual		21.3109

Fit Statistics

-2 Res Log Likelihood	3311.4
AIC (smaller is better)	3315.4
AICC (smaller is better)	3315.4
BIC (smaller is better)	3321.0

5. Random Intercepts and Random Slopes Model

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	id	7.8502
UN(2,1)	id	0.2533
UN(2,2)	id	1.1440
Residual		9.7713

Fit Statistics

-2 Res Log Likelihood	3098.9
AIC (smaller is better)	3106.9
AICC (smaller is better)	3106.9
BIC (smaller is better)	3118.0

EXHIBIT B

i. Means Profile Model

Fit Statistics (ML)

-2 Log Likelihood	3071.2
AIC (smaller is better)	3131.2

Solution for Fixed Effects (REML)

Effect	trt	week	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			27.3025	0.6945	117	39.31	<.0001
trt	3		-0.03250	0.9822	117	-0.03	0.9737
trt	2		0.02500	0.9822	117	0.03	0.9797
trt	1		0	.	.	.	.
week		8	-2.8040	1.4820	117	-1.89	0.0610
week		6	-2.1073	1.3097	117	-1.61	0.1103
week		4	-1.8079	1.0704	117	-1.69	0.0939
week		2	-1.1359	0.7556	117	-1.50	0.1355
week		0	0	.	.	.	.
trt*week	3	8	-5.7414	2.1044	117	-2.73	0.0073
trt*week	3	6	-3.7425	1.8414	117	-2.03	0.0444
trt*week	3	4	-2.8708	1.5100	117	-1.90	0.0597
trt*week	3	2	-0.9895	1.0687	117	-0.93	0.3564
trt*week	3	0	0	.	.	.	.
trt*week	2	8	-3.9920	2.1008	117	-1.90	0.0599
trt*week	2	6	-3.0036	1.8316	117	-1.64	0.1037
trt*week	2	4	-3.1903	1.5139	117	-2.11	0.0372
trt*week	2	2	0.3119	1.0963	117	0.28	0.7765
trt*week	2	0	0	.	.	.	.
trt*week	1	8	0	.	.	.	.
trt*week	1	6	0	.	.	.	.
trt*week	1	4	0	.	.	.	.
trt*week	1	2	0	.	.	.	.
trt*week	1	0	0	.	.	.	.

Type 3 Tests of Fixed Effects (REML)

Effect	Num DF	Den DF	F Value	Pr > F
trt	2	117	2.54	0.0833
week	4	117	13.19	<.0001
trt*week	8	117	1.68	0.1116

ii. Linear Trend Model

Fit Statistics (ML)

-2 Log Likelihood	3082.6
AIC (smaller is better)	3124.6

Solution for Fixed Effects (REML)

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		27.0501	0.5775	117	46.84	<.0001
trt	3	0.2060	0.8174	117	0.25	0.8015
trt	2	0.1970	0.8204	117	0.24	0.8107
trt	1	0	.	.	.	.
week		-0.3367	0.1839	117	-1.83	0.0696
week*trt	3	-0.7072	0.2612	117	-2.71	0.0078
week*trt	2	-0.4692	0.2608	117	-1.80	0.0746
week*trt	1	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	2	117	0.04	0.9603
week	1	117	46.66	<.0001
week*trt	2	117	3.80	0.0251

iii. Linear Trend Model without trt*week interactions

Fit Statistics (ML)

-2 Log Likelihood	3090.1
AIC (smaller is better)	3128.1

Solution for Fixed Effects (REML)

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		27.2300	0.5752	117	47.34	<.0001
trt	3	-0.1337	0.8103	117	-0.17	0.8692
trt	2	-0.02183	0.8136	117	-0.03	0.9786
trt	1	0	.	.	.	.
week		-0.7220	0.1092	117	-6.61	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
trt	2	117	0.02	0.9845
week	1	117	43.71	<.0001

iv. Linear Trend Model without trt*week and trt terms

Fit Statistics (ML)

-2 Log Likelihood	3090.2
AIC (smaller is better)	3124.2

Solution for Fixed Effects (REML)

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	27.1793	0.3327	119	81.70	<.0001
week	-0.7229	0.1092	119	-6.62	<.0001

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
week	1	119	43.82	<.0001

EXHIBIT C: Random Intercepts and Slopes Model

Estimated G Matrix

Row	Effect	id	Col1	Col2
1	Intercept	1	7.8502	0.2533
2	week	1	0.2533	1.1440

Estimated G Correlation Matrix

Row	Effect	id	Col1	Col2
1	Intercept	1	1.0000	0.08453
2	week	1	0.08453	1.0000

Estimated V Matrix for id 1

Row	Col1	Col2	Col3	Col4	Col5
1	94.8893	66.3077	47.4974	28.6871	9.8768
2	66.3077	61.8446	37.8389	23.6046	9.3702
3	47.4974	37.8389	37.9518	18.5220	8.8635
4	28.6871	23.6046	18.5220	23.2108	8.3569
5	9.8768	9.3702	8.8635	8.3569	17.6216

Estimated V Correlation Matrix for id 1

Row	Col1	Col2	Col3	Col4	Col5
1	1.0000	0.8656	0.7915	0.6113	0.2415
2	0.8656	1.0000	0.7810	0.6230	0.2838
3	0.7915	0.7810	1.0000	0.6241	0.3427
4	0.6113	0.6230	0.6241	1.0000	0.4132
5	0.2415	0.2838	0.3427	0.4132	1.0000

Solution for Fixed Effects

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept		27.0347	0.5936	117	45.54	<.0001
trt	3	0.1220	0.8402	286	0.15	0.8846

trt	2	0.2605	0.8449	286	0.31	0.7581
trt	1	0	.	.	.	.
week		−0.3187	0.1888	117	−1.69	0.0941
week*trt	3	−0.6965	0.2678	286	−2.60	0.0098
week*trt	2	−0.5631	0.2676	286	−2.10	0.0362
week*trt	1	0	.	.	.	.

Solution for Random Effects

Effect	id	Estimate	Std Err Pred	DF	t Value	Pr > |t|
Intercept	1	2.9926	1.7746	286	1.69	0.0928
week	1	2.2607	0.4155	286	5.44	<.0001
Intercept	2	−0.3605	1.7746	286	−0.20	0.8392
week	2	1.3566	0.4155	286	3.27	0.0012
Intercept	3	−1.4265	1.7768	286	−0.80	0.4227
week	3	0.3657	0.4431	286	0.83	0.4099
Intercept	4	−0.3196	1.7746	286	−0.18	0.8572
week	4	0.1419	0.4155	286	0.34	0.7329

$\alpha = 0.05$ 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 $p < 0.05$.