BIO 226: APPLIED LONGITUDINAL ANALYSIS

LECTURE 6

Modelling Longitudinal Data

Analysis of Response Profiles

Modelling Longitudinal Data

Overview:

Longitudinal data present two aspects of the data that require modelling:

(1) mean response over time

(2) covariance among repeated measures

Models for longitudinal data must jointly specify models for the mean and covariance.

Modelling the Mean

Two main approaches can be distinguished:

(1) analysis of response profiles

(2) parametric or semi-parametric curves

Modelling the Covariance

Three broad approaches can be distinguished:

(1) "unstructured" or arbitrary pattern of covariance

(2) covariance pattern models

(3) random effects covariance structure

Modelling the Mean: Analysis of Response Profiles

Basic idea: Compare groups of subjects in terms of mean response profiles over time.

Useful for *balanced* longitudinal designs and when there is a single categorical covariate (perhaps denoting different treatment or exposure groups).

Analysis of response profiles can be extended to handle more than a single group factor.

Analysis of response profiles can also handle missing data.

Example

Treatment of Lead-Exposed Children (TLC) Trial

Recall data from TLC trial:

Children randomized to placebo or Succimer.

Measures of blood lead level at baseline, 1, 4 and 6 weeks.

The sequence of means over time in each group is referred to as the "mean response profile".

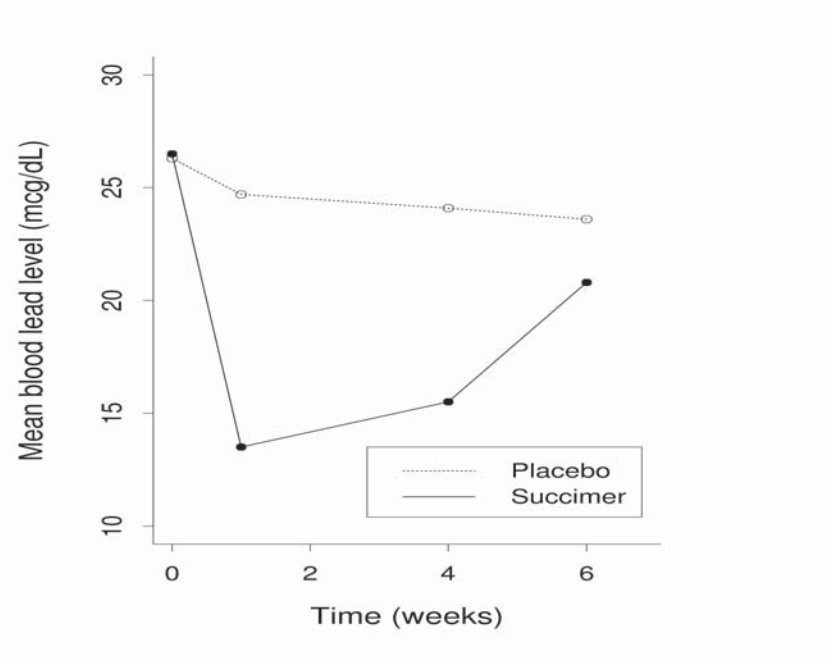

Figure 1: Mean blood lead levels at baseline, week 1, week 4, and week 6 in the succimer and placebo groups.

Hypotheses concerning response profiles

Given a sequence of n repeated measures on a number of distinct groups of individuals, three main questions:

(1) Are the mean response profiles similar in the groups, in the sense that the mean response profiles are parallel?
This is a question that concerns the *group* $\times$ *time interaction effect*.

(2) Assuming mean response profiles are parallel, are the means constant over time, in the sense that the mean response profiles are flat?
This is a question that concerns the *time effect*.

(3) Assuming that the population mean response profiles are parallel, are they also at the same level in the sense that the mean response profiles for the groups coincide?
This is a questions that concerns the *group effect*;

Note: For many longitudinal studies, especially longitudinal clinical trials, main interest is in Question 1: *group* $\times$ *time interaction effect*.

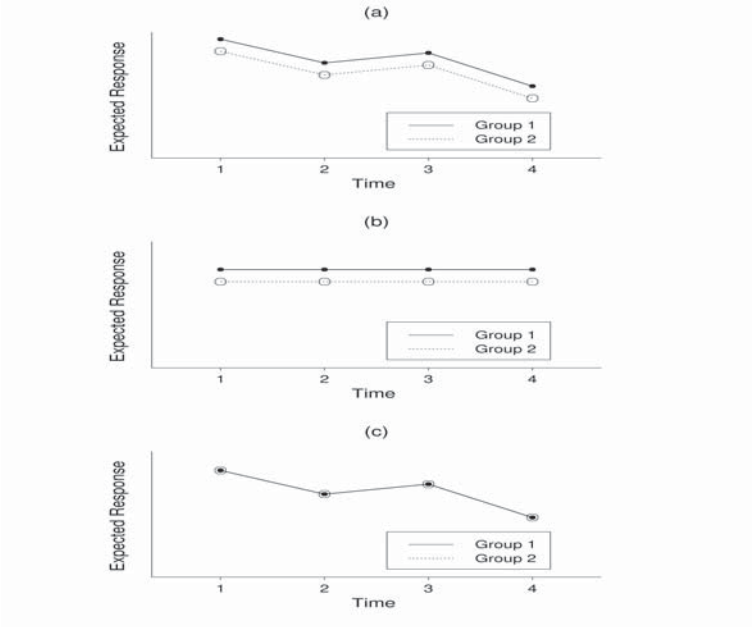

Figure 2: Graphical representation of the null hypotheses of (a) no group $\times$ time interaction effect, (b) no time effect, and (c) no group effect.

Table 1: Mean response profile over time in 2 groups.

	Measurement Occasion			
Group	1	2	...	n
1	$\mu_1(1)$	$\mu_2(1)$	...	$\mu_n(1)$
2	$\mu_1(2)$	$\mu_2(2)$	...	$\mu_n(2)$

Next, consider the differences between the group means at each occasion.

Define $\Delta_j = \mu_j(1) - \mu_j(2), \quad j = 1, ..., n.$

The first hypothesis in an analysis of response profiles can be expressed as:

No *group* $\times$ *time interaction effect*:

$$H_0 : \Delta_1 = \Delta_2 = \cdots = \Delta_n.$$

With only 2 groups, the test of the null hypothesis of no group $\times$ time interaction effect has $(n-1)$ degrees of freedom.

Note: Rejection of H_0, no *group* $\times$ *time interaction*, indicates groups differ in their patterns of change over time, but does not indicate how they differ.

Table 2: Mean response profile over time in G groups.

	Measurement Occasion			
Group	1	2	...	n
1	$\mu_1(1)$	$\mu_2(1)$	...	$\mu_n(1)$
2	$\mu_1(2)$	$\mu_2(2)$	...	$\mu_n(2)$
⋮	⋮	⋮		⋮
g	$\mu_1(g)$	$\mu_2(g)$	...	$\mu_n(g)$
⋮	⋮	⋮		⋮
G	$\mu_1(G)$	$\mu_2(G)$	...	$\mu_n(G)$

Let G denote the number of groups, with $G \geq 2$.

Define $\Delta_j(g) = \mu_j(g) - \mu_j(G), j = 1, ..., n; g = 1, ..., G-1$.

With $G \geq 2$, the test of the null hypothesis of no group $\times$ time interaction effect can be expressed as:

No *group* $\times$ *time interaction effect*:

$$H_{01} : \Delta_1(g) = \Delta_2(g) = \cdots = \Delta_n(g); \quad \text{for} \;\; g = 1, ..., G-1.$$

With $G \geq 2$, the test of the null hypothesis of no group $\times$ time interaction effect has $(G-1) \times (n-1)$ degrees of freedom.

Remark on Baseline Measurement

Baseline measurement given same status as post-randomization outcomes.

Alternative methods:

1. Subtract baseline from each subsequent observation and analyze differences

2. Use baseline as a covariate

Method 2 is generally more efficient than Method 1 for pre-test post-test designs[1] but both require discarding subjects if there are missing baseline values.

[1] In the next lecture, we discuss alternative methods for handling baseline response.

Model for Variance-Covariance Matrix: Unstructured

Table 3: Assumed covariance matrix in analysis of response profiles.

Covariance Matrix				
σ_1^2	σ_{12}	σ_{13}	$\cdots$	σ_{1n}
σ_{21}	σ_2^2	σ_{23}	$\cdots$	σ_{2n}
σ_{31}	σ_{32}	σ_3^2	$\cdots$	σ_{3n}
$\vdots$	$\vdots$	$\vdots$	$\ddots$	$\vdots$
σ_{n1}	σ_{n2}	σ_{n3}	$\cdots$	σ_n^2

Testing Whether the Mean Response Profiles are Parallel

The main focus of analysis is on a global test of the null hypothesis that the mean response profiles are parallel among the groups.

This translates into a hypothesis concerning regression coefficients for the *group* $\times$ *time interaction* being equal to zero.

In testing this hypothesis, both *group* and *time* are regarded as categorical covariates (analogous to two-way ANOVA).

The analysis of response profiles can be specified as a regression model with "indicator variables" for *group* and *time*.

However, unlike standard regression, the correlation and variability among repeated measures on the same individuals must be properly accounted for.

Beyond testing the null hypothesis of parallel profiles, the estimated regression coefficients have meaningful interpretations.

Case Study

Analysis of Response Profiles

Treatment of Lead-Exposed Children Trial

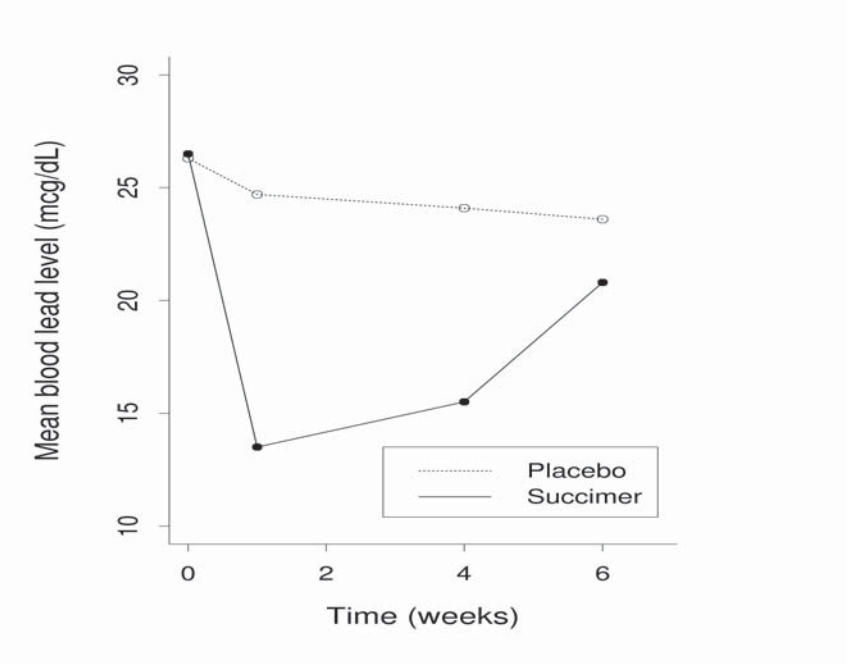

Figure 3: Plot of mean blood lead levels at baseline, week 1, week 4, and week 6 in the succimer and placebo groups.

Recall, the main focus of analysis is on a global test of the null hypothesis that the mean response profiles are similar in the groups.

Are the mean response profiles parallel?

This is a question that concerns the *group* $\times$ *time interaction effect*.

In testing this hypothesis, both *group* and *time* are regarded as categorical covariates (analogous to two-way ANOVA).

The analysis of response profiles can be specified as a regression model with "indicator variables" for *group* and *time*.

Choice of Reference Level

The usual choice of reference group:

(i) A natural baseline or comparison group, and/or

(ii) group with largest sample size

In longitudinal data setting, the "baseline" or first measurement occasion is a natural reference group for "time".

Treatment of Lead-Exposed Children Trial

In the TLC Trial there are two groups (placebo and succimer) and four measurement occasions (week 0, 1, 4, 6).

Let $X_1 = 1$ for all children at all occasions.

Creating indicator variables for group and time:

Group:

Let $X_2 = 1$ if child randomized to succimer, $X_2 = 0$ otherwise.

Time:

Let $X_3 = 1$ if measurement at week 1, $X_3 = 0$ otherwise
Let $X_4 = 1$ if measurement at week 4, $X_4 = 0$ otherwise
Let $X_5 = 1$ if measurement at week 6, $X_5 = 0$ otherwise

Recall: Hypothesis of main interest concerns *group* $\times$ *time interaction effect*.

Analysis of response profiles model can be expressed as:

$$Y = \beta_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_2 * X_3 + \beta_7 X_2 * X_4 + \beta_8 X_2 * X_5 + e$$

Test of *group* $\times$ *time interaction*: $H_0 : \beta_6 = \beta_7 = \beta_8 = 0$.

The analysis must also account for the correlation among repeated measures on the same child.

The analysis of response profiles estimates separate variances for each occasion (4 variances) and six pairwise correlations.

Treatment of Lead-Exposed Children Trial

Table 4 displays estimates of the covariance matrix.

Note the discernible increase in the variability in blood lead levels from pre- to post-randomization.

This increase in variability from baseline is probably due to:

(1) given the treatment group assignment, there may be natural heterogeneity in the individual response trajectories over time,

(2) the trial had an inclusion criterion that blood lead levels at baseline were in the range of 20-44 micrograms/dL.

Table 4: Estimated covariance matrix for the blood lead levels at baseline, week 1, week 4, and week 6 for the children from the TLC trial.

Covariance Matrix			
25.2	19.1	19.7	22.2
19.1	44.3	35.5	29.7
19.7	35.5	47.4	30.6
22.2	29.7	30.6	58.7

Table 5: Estimated correlation matrix for the blood lead levels at baseline, week 1, week 4, and week 6 for the children from the TLC trial.

Correlation Matrix			
1.00	0.57	0.57	0.58
0.57	1.00	0.78	0.58
0.57	0.78	1.00	0.58
0.58	0.58	0.58	1.00

Table 6: Tests of fixed effects based on analysis of response profiles of the blood lead level data at baseline, weeks 1, 4, and 6.

Variable	DF	Chi-Squared	*P*-Value
Group	1	25.43	<0.0001
Week	3	184.48	<0.0001
Group × Week	3	107.79	<0.0001

Test of the group × time interaction is based on (multivariate) Wald test (comparison of estimates to SEs).

In the TLC trial, question of main interest concerns comparison of two treatment groups in terms of their patterns of change from baseline.

This question translates into test of group × time interaction.

The test of the group × time interaction yields a Wald statistic of 107.79 with 3 degrees of freedom ($p < 0.0001$).

Because this is a global test, it indicates that groups differ but does not tell us how they differ.

Recall, analysis of response profiles model can be expressed as:

$$Y = \beta_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_2 * X_3 + \beta_7 X_2 * X_4 + \beta_8 X_2 * X_5 + e$$

Test of *group* $\times$ *time interaction*: $H_0 : \beta_6 = \beta_7 = \beta_8 = 0$.

The 3 single df contrasts for group $\times$ time interaction have direct interpretations in terms of group comparisons of changes from baseline.

They indicate that children treated with succimer have greater decrease in mean blood lead levels from baseline at all occasions when compared to children treated with placebo (see Table 7).

Table 7: Estimated regression coefficients and standard errors based on analysis of response profiles of the blood lead level data.

Variable	Group	Week	Estimate	SE	Z
Intercept			26.272	0.710	36.99
Group	A		0.268	1.005	0.27
Week		1	−1.612	0.792	−2.04
Week		4	−2.202	0.815	−2.70
Week		6	−2.626	0.889	−2.96
Group × Week	A	1	−11.406	1.120	−10.18
Group × Week	A	4	−8.824	1.153	−7.66
Group × Week	A	6	−3.152	1.257	−2.51

Strengths and Weaknesses of Analysis of Response Profiles

Strengths:

Allows arbitrary patterns in the mean response over time (no time trend assumed) and arbitrary patterns in the covariance.

Analysis has a certain robustness since potential risks of bias due to misspecification of models for mean and covariance are minimal.

Can accommodate an arbitrary pattern of missingness.

Drawbacks:

Requirement that the longitudinal design be balanced.

Analysis cannot incorporate mistimed measurements.

Analysis ignores the time-ordering (time trends) of the repeated measures in a longitudinal study.

Produces omnibus tests of effects that may have low power to detect group differences in specific trends in the mean response over time (e.g., linear trends in the mean response).

The number of estimated parameters, $G \times n$ mean parameters and $\frac{n(n+1)}{2}$ covariance parameters (variances and correlations), grows rapidly with the number of measurement occasions.

Summary

"Analysis of response profiles" can be framed as a linear regression with correlated observations.

Extensions beyond the usual profile analysis:

time contrasts

area-under-the-curve-analyses

baseline covariates

missing observations

Analyzing the TLC data in SAS

```
data tlc;
  infile 'tlc.txt';
  input id group $ y1 y2 y3 y4;
run;

data tlc1;
  set tlc;
  y=y1; time=0; output;
  y=y2; time=1; output;
  y=y3; time=4; output;
  y=y4; time=6; output;
  drop y1-y4;
run;
```

```
proc sort; by group descending time;
run;

proc mixed order=data;
  class id group time;
  model y=group time group*time/s chisq;
  repeated time/type=un subject=id r rcorr;
run;
```


The Mixed Procedure

Model Information

Data Set	WORK.TLC1
Dependent Variable	y
Covariance Structure	Unstructured
Subject Effect	id
Estimation Method	REML
Residual Variance Method	None
Fixed Effects SE Method	Model-Based
Degrees of Freedom Method	Between-Within

Class Level Information

Class	Levels	Values
id	100	2 3 5 6 12 14 19 20 22 23 25 26 27 29 31 32 36 39 40 43 44 45 48 49 53 54 57 64 65 66 68 69 70 71 72 79 82 85 87 89 90 91 93 94 95 96 97 98 99 100 1 4 7 8 9 10 11 13 15 16 17 18 21 24 28 30 33 34 35 37 38 41 42 46 47 50 51 52 55 56 58 59 60 61 62 63 67 73 74 75 76 77 78 80 81 83 84 86 88 92
group	2	A P
time	4	6 4 1 0

Dimensions

Covariance Parameters	10
Columns in X	15
Columns in Z	0
Subjects	100
Max Obs Per Subject	4

Number of Observations

Number of Observations Read	400
Number of Observations Used	400
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	2626.25517748	
1	1	2416.07594087	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated R Matrix for id 2

Row	Col1	Col2	Col3	Col4
1	58.6510	30.6205	29.6750	22.2016
2	30.6205	47.3778	35.5351	19.6995
3	29.6750	35.5351	44.3458	19.1074
4	22.2016	19.6995	19.1074	25.2257

Estimated R Correlation Matrix for id 2

Row	Col1	Col2	Col3	Col4
1	1.0000	0.5809	0.5819	0.5772
2	0.5809	1.0000	0.7753	0.5698
3	0.5819	0.7753	1.0000	0.5713
4	0.5772	0.5698	0.5713	1.0000

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	id	58.6510
UN(2,1)	id	30.6205
UN(2,2)	id	47.3778
UN(3,1)	id	29.6750
UN(3,2)	id	35.5351
UN(3,3)	id	44.3458
UN(4,1)	id	22.2016
UN(4,2)	id	19.6995
UN(4,3)	id	19.1074
UN(4,4)	id	25.2257

Fit Statistics

-2 Res Log Likelihood	2416.1
AIC (smaller is better)	2436.1
AICC (smaller is better)	2436.7
BIC (smaller is better)	2462.1

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
9	210.18	<.0001

Solution for Fixed Effects

Effect	group	time	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept			26.2720	0.7103	98	36.99	<.0001
group	A		0.2680	1.0045	98	0.27	0.7902
group	P		0	.	.	.	.
time		6	-2.6260	0.8885	98	-2.96	0.0039
time		4	-2.2020	0.8149	98	-2.70	0.0081
time		1	-1.6120	0.7919	98	-2.04	0.0445
time		0	0	.	.	.	.
group*time	A	6	-3.1520	1.2566	98	-2.51	0.0138
group*time	A	4	-8.8240	1.1525	98	-7.66	<.0001
group*time	A	1	-11.4060	1.1199	98	-10.18	<.0001
group*time	A	0	0	.	.	.	.
group*time	P	6	0	.	.	.	.
group*time	P	4	0	.	.	.	.
group*time	P	1	0	.	.	.	.
group*time	P	0	0	.	.	.	.

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	Chi-Square	F Value	Pr > ChiSq	Pr > F
group	1	98	25.43	25.43	<.0001	<.0001
time	3	98	184.48	61.49	<.0001	<.0001
group*time	3	98	107.79	35.93	<.0001	<.0001