BIO 226: APPLIED LONGITUDINAL ANALYSIS

LECTURE 7

Adjustment for Baseline Response

Weaknesses of Profile Analysis

Recall: A drawback of analysis of response profiles is that it ignores the time-ordering (time trends) of the repeated measures in a longitudinal study.

Moreover, it produces omnibus tests of effects that may have low power to detect group differences in specific trends in the mean response over time.

In a certain sense, an omnibus test disperses statistical power among too many alternatives.

This lack of specificity is potentially a problem in studies with a large number of measurement occasions.

Recall that the test for group $\times$ time interaction has $(G-1)\times(n-1)$ degrees of freedom.

This general test becomes less sensitive to an interaction with a specific pattern as n increases.

Adjustment for Baseline Response

Another way to accommodate the baseline is to "adjust for baseline" in the analysis by treating it as a covariate.

That is, include only the post-baseline measures $(Y_{i2}, Y_{i3}, \ldots, Y_{in})$ in the response vector, and model these outcomes as

$$Y_{ij} = X_{ij}'\beta + \beta_{p+1}Y_{i1} + e_{ij}, \;\; j = 2, \ldots, n.$$

Including the baseline measurement as a covariate is often referred to as "Analysis of Covariance" (ANCOVA).

When, if ever, is it more preferable to use ANCOVA in favor of a profile analysis in which Y_{i1} is included in the response vector?

The answer depends on the study design: observational versus randomized study.

For observational study, usually not advisable to employ ANCOVA approach because baseline value may be associated with other variables whose effects are to be studied.

Example: Observational study comparing rates of decline of pulmonary function in asthmatics and non-asthmatics.

Suppose asthmatics have lower pulmonary function at all ages, but rates of decline are equal for asthmatics and non-asthmatics.

Suppose the model that best describes the data is:

$$Y_{ij} = \beta_1 + \beta_2 \text{Asthma}_i + \beta_3 \text{Age}_{ij} + e_{ij}$$

Thus the model for the non-asthmatics is,

$$E(Y_{ij}) = \beta_1 + \beta_3 \text{Age}_{ij}$$

and the model for the asthmatics is,

$$E(Y_{ij}) = (\beta_1 + \beta_2) + \beta_3 \text{Age}_{ij}$$

Clearly, the rate of change or decline, expressed by β_3, is the same in the two groups.

As a result, an analysis that compares the decline in the two groups would conclude that there are no differences.

However, if we introduce the baseline value as a covariate and want to test whether the rate of decline varies by asthma status, the model is:

$$Y_{ij} = \beta_1 + \beta_2 \text{Asthma}_i + \beta_3 \text{Age}_{ij} + \beta_4 \text{Asthma}_i * \text{Age}_{ij} + \beta_5 Y_{i1} + e_{ij}$$

This model gives the predicted values for asthmatics and non-asthmatics relative to a common baseline value.

As a result, the decline in pulmonary function for the asthmatics will appear to be greater than the decline for the non-asthmatics.

Why?

Note that the analysis with baseline value as a covariate addresses a somewhat different question.

It considers the conditional question:

"Is an asthmatic expected to show the same decline in pulmonary function as a non-asthmatic, given they both have the same initial level of pulmonary function?"

The answer to this question is a resounding "No".

The asthmatic will be expected to decline more.

Why?

If the asthmatic is initially at the same level of pulmonary function as the non-asthmatic,

(1) either the asthmatic's level of function is very high and can be expected to decline or regress to the mean level for asthmatics, or

(2) the non-asthmatic's level of function is very low and can be expected to increase or regress to the mean level for non-asthmatics

As a result, the rates of decline, conditional on the same initial value, will not be the same in the two groups.

When subjects have been randomized to groups and the baseline value has been obtained before any interventions, adjustment for baseline through ANCOVA is of interest.

In a randomized study, the mean response at baseline is independent of treatment assignment.

In that setting, it can be shown that a test based on a contrast using the full vector and the test based on ANCOVA represent alternative tests of the same null hypothesis.

Moreover, the ANCOVA approach will always be more efficient, yielding estimates of treatment group effects with smaller standard errors than those obtained by calculating contrasts.

ANCOVA: Greater Efficiency

The greater efficiency of ANCOVA can be highlighted by examining the relative efficiency (or ratio of variances) in simple settings.

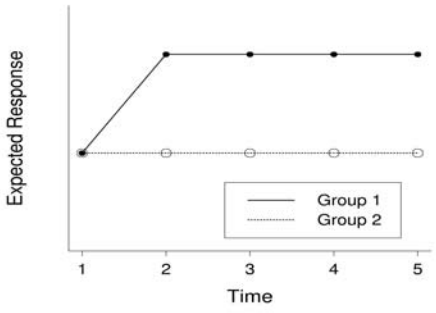

Figure 1: Suppose changes in the mean response from baseline (in Group 1) that persist throughout the duration of follow up.

When data are complete (no missing data), a "one-degree-of-freedom test" can be constructed as follows:

(1) calculate a univariate summary statistic for each subject

(2) perform a test for equality of means of these summary statistics in the G groups (e.g., t-test, ANOVA).

A reasonable approach for this setting is to test for equality of mean response minus baseline, the summary statistic for i^{th} subject is

$$\frac{(Y_{i2} + Y_{i3} + \cdots + Y_{in})}{n-1} - Y_{i1}.$$

This analysis compares the average of post-treatment values to pre-treatment.

One then compares the means of these univariate statistics across groups.

Alternatively, the ANCOVA model for this setting does not subtract off Y_{i1}, but rather controls for it as a covariate:

$$Y_i^* = \beta_1 + \beta_2 Y_{i1} + \beta_3 \texttt{trt}_i + e_i^*,$$

where

$$Y_i^* = \frac{(Y_{i2} + Y_{i3} + \cdots + Y_{in})}{n-1},$$

$\texttt{trt}_\texttt{i}$ is an indicator for group, and e_i^* is the error term in the univariate model.

The ANOVA or ANCOVA analysis will be appealing where initial changes from baseline are expected to persist throughout the duration of follow up (see Figure 1).

Suppose the variance is homogeneous, with common variance σ^2, and the correlation between any pair of repeated measures is ρ, the relative efficiency of the ANCOVA model is:

$$\frac{1}{n}\left\{1 + (n-1)\,\rho\right\}.$$

The greater efficiency of ANCOVA depends on both the number of repeated measures and magnitude of ρ.

For example, when $n = 5$ and $\rho = 0.4$ the analysis of covariance is approximately twice as efficient as subtracting the baseline response.

Alternative Adjustments for Baseline Response

The notion of adjustment for baseline can be applied more generally in the analysis of response profiles.

We consider four ways of handling the baseline value:

(1) Retain it as part of the outcome vector and make no assumptions about group differences in the mean response at baseline.

(2) Retain it as part of the outcome vector and assume the group means are equal at baseline, as might be appropriate in a randomized trial.

(3) Subtract the baseline response from all of the remaining post-baseline responses, and analyze the differences from baseline.

(4) Use baseline value as a covariate in the analysis of the post-baseline responses.

The first method retains the baseline response as part of the outcome vector.

This method produces the standard analysis of response profile results (see Tables 2 and 3).

The test of the group $\times$ time interaction from this model yields a Wald statistic of 107.79, with 3 degrees of freedom.

Table 1: Tests of fixed effects based on a profile analysis 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 $\times$ Week	3	107.79	<0.0001

Table 2: 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 $\times$ Week	A	1	-11.406	1.120	-10.18
Group $\times$ Week	A	4	-8.824	1.153	-7.66
Group $\times$ Week	A	6	-3.152	1.257	-2.51

The second method also retains the baseline response as part of the outcome vector.

This method corresponds to an analysis of response profiles where the group means at baseline are constrained to be equal.

Implemented by excluding the treatment group main effect from the model for the response profiles (see Table 4).

Note: Baseline (week 0) must be chosen as the reference level for time.

The test of the group $\times$ time interaction yields a Wald statistic of 111.96, with 3 degrees of freedom.

Table 3: Estimated regression coefficients and standard errors based on an analysis of response profiles of the blood lead level data assuming equal mean blood lead levels at baseline.

Variable	Group	Week	Estimate	SE	Z
Intercept			26.406	0.500	52.83
Week		1	−1.645	0.782	−2.10
Week		4	−2.231	0.807	−2.76
Week		6	−2.642	0.887	−2.98
Group $\times$ Week	A	1	−11.341	1.093	−10.38
Group $\times$ Week	A	4	−8.765	1.131	−7.75
Group $\times$ Week	A	6	−3.120	1.251	−2.49

The third method does not retain the baseline response as part of the outcome vector.

Baseline response is subtracted from post-baseline responses and analysis is based on these differences from baseline,

$$D_i = (Y_{i2} - Y_{i1}, Y_{i3} - Y_{i1}, \ldots, Y_{in} - Y_{i1})'.$$

Because outcome is a change score, this alters interpretation of the tests for all three effects.

Test for group $\times$ time interaction becomes a test for parallel profiles for the *changes* from baseline.

Test for group effect becomes a test that *changes* from baseline at occasion 2 are the same across groups (assuming occasion 2 is reference level).

Table 4: Estimated regression coefficients and standard errors based on an analysis of response profiles of the changes from baseline in blood lead levels at week 1, week 4, and week 6.

Variable	Group	Week	Estimate	SE	Z
Intercept			-1.612	0.792	-2.04
Group	A		-11.406	1.120	-10.18
Week		4	-0.590	0.643	-0.92
Week		6	-1.014	0.934	-1.09
Group $\times$ Week	A	4	2.582	0.909	2.84
Group $\times$ Week	A	6	8.254	1.321	6.25

Thus, the original test of "parallelism of profiles" now becomes a joint test of main effect of group and the group $\times$ time interaction.

Formally equivalent to the test of parallelism in standard analysis of response profiles.

Thus, first and third methods are completely equivalent.

The fourth method does not retain the baseline response as part of the outcome vector.

Instead, it focuses on *adjusted* changes from baseline and restricts the outcome vector to measurements obtained post-baseline.

Similar to the third method, test of interest is a joint test of main effect of group and the group $\times$ time interaction.

This yields a Wald statistic of 111.13, with 3 degrees of freedom.

Table 5: Estimated regression coefficients and standard errors based on an analysis of response profiles of the adjusted changes from baseline in blood lead levels at week 1, week 4, and week 6.

Variable	Group	Week	Estimate	SE	Z
Intercept			-1.638	0.777	-2.11
Baseline† $(Y_{i1} - 26.406)$			-0.196	0.094	-2.08
Group	A		-11.354	1.099	-10.34
Week		4	-0.590	0.643	-0.92
Week		6	-1.014	0.934	-1.09
Group $\times$ Week	A	4	2.582	0.909	2.84
Group $\times$ Week	A	6	8.254	1.321	6.25

†Centering baseline response on its overall mean (26.406) gives the intercept a meaningful interpretation.

Summary

In general, randomized studies are the only setting where we recommend adjustment for baseline through analysis of covariance.

In randomized studies, such an adjustment leads to meaningful tests of hypothesis of scientific interest.

Moreover, the tests based on the analysis of covariance approach will be more powerful.

Alternatively, and almost equivalently, can retain baseline as part of outcome vector and assume group means are equal at baseline.

Not advisable to make the above adjustments in observational studies.