BIO 226: APPLIED LONGITUDINAL ANALYSIS

LECTURE 10

Mixed Effects Models for Longitudinal Data

Two-Stage (Two-Level) Random Effects Formulation

Two-Stage (Two-Level) Formulation

Linear mixed effects models can be motivated in terms of the following two-stage formulation of the model.

Basic idea: In the two-stage formulation of the model, we assume

1. A straight line (or more generally a "growth" curve) fits the observed responses for each subject (**first stage or level**)

2. A regression model relating the mean of the individual intercepts and slopes to subject-specific covariates (**second stage or level**)

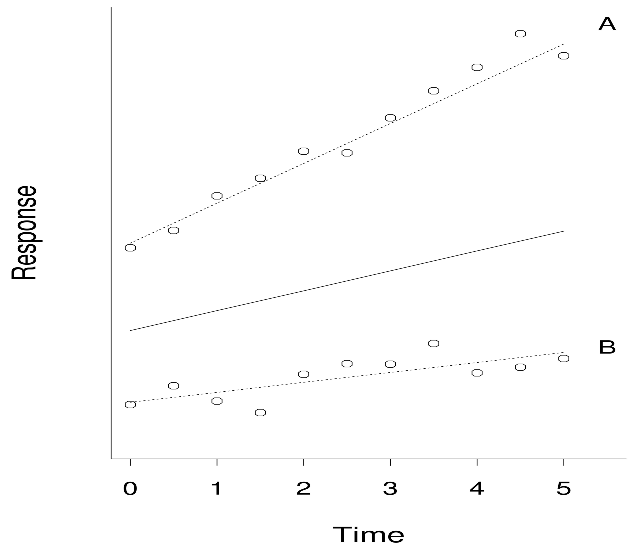

Figure 1: Graphical representation of the overall and subject-specific mean responses over time, plus measurement errors.

Stage 1

In the first stage, each subject is assumed to have their own unique individual-specific mean response trajectory. So for subject i:

$$Y_{ij} = Z'_{ij}\beta_i + \epsilon_{ij}, \quad (j = 1, ..., n_i)$$

where β_i is a vector of subject-specific regression parameters; the errors, ϵ_{ij}, are (usually) assumed to be independent within a subject.

For example, a simple model with subject-specific intercepts and slopes over time is given by

$$Y_{ij} = \beta_{1i} + \beta_{2i}t_{ij} + \epsilon_{ij}.$$

Thus, in stage 1 we posit a regression model with separate or distinct coefficients for each subject.

This is equivalent to considering separate linear regression models for the data for each subject.

Note: Covariates in Z_{ij} are restricted to covariates that vary within the subject over time (i.e. time-varying covariates), except for the column of 1's for the intercept.

Time-invariant or between-subject covariates (e.g., gender, treatment group, exposure group) cannot be included in Z_{ij}; instead, they are introduced in the second stage of the model formulation.

Stage 2

In the second stage, we assume that the subject-specific effects, the β_i's, are random (i.e. there is some distribution for the β_i's in the population, e.g. a normal distribution).

The mean and covariance of the β_i's are the population parameters that are modelled in the second stage.

Specifically, variation in the β_i's in the population is described in terms of between-subject covariates, say A_i (e.g., gender, treatment group):

$$\beta_i = A_i\beta + b_i, \text{ where } b_i \sim N(0, G).$$

For example, consider two-group (e.g. treatment vs. control) setting and the simple model with subject-specific intercepts and slopes.

Allowing both the mean intercept and slope to depend on group

$$\begin{aligned} E(\beta_{1i}) &= \beta_1 + \beta_2\,\texttt{Group}_\texttt{i} \\ E(\beta_{2i}) &= \beta_3 + \beta_4\,\texttt{Group}_\texttt{i} \end{aligned}$$

where $\texttt{Group}_\texttt{i} = \texttt{1}$ if the i^{th} individual was assigned to the treatment, and $\texttt{Group}_\texttt{i} = \texttt{0}$ otherwise.

In this model, β_1 is the mean intercept in the control group, while $\beta_1 + \beta_2$ is the mean intercept in the treatment group.

Similarly, β_3 is the mean slope in the control group, while $\beta_3 + \beta_4$ is the mean slope in the treatment group.

In this model, the design matrix A_i of between-subject covariates has the following form:

$$A_i = \begin{pmatrix} 1 & \texttt{Group}_\texttt{i} & 0 & 0 \\ 0 & 0 & 1 & \texttt{Group}_\texttt{i} \end{pmatrix}.$$

Thus, for the control group, the model for the mean is

$$E\begin{pmatrix} \beta_{1i} \\ \beta_{2i} \end{pmatrix} = \begin{pmatrix} 1 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix} \begin{pmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{pmatrix} = \begin{pmatrix} \beta_1 \\ \beta_3 \end{pmatrix};$$

and similarly, for the treatment group, the model for the mean is

$$E\begin{pmatrix}\beta_{1i}\\ \beta_{2i}\end{pmatrix} = \begin{pmatrix}1 & 1 & 0 & 0\\ 0 & 0 & 1 & 1\end{pmatrix}\begin{pmatrix}\beta_1\\ \beta_2\\ \beta_3\\ \beta_4\end{pmatrix} = \begin{pmatrix}\beta_1+\beta_2\\ \beta_3+\beta_4\end{pmatrix}.$$

It is also assumed that there is residual variation in the β_i's, that cannot be explained by the effect of group.

As $\beta_i = A_i\beta + b_i$, this is the variability in the b_i's given by

$$\text{Cov}(\beta_i|A_i) = \text{Cov}(b_i) = G = \begin{pmatrix} g_{11} & g_{12}\\ g_{21} & g_{22}\end{pmatrix},$$

where $g_{11} = \text{Var}(b_{1i})$, $g_{22} = \text{Var}(b_{2i})$, and $g_{12} = g_{21} = \text{Cov}(b_{1i}, b_{2i})$.

Thus, g_{11} is the variance of β_{1i}, after adjusting for the effect of treatment group, and so on.

Two-Stage Analysis: "NIH Method"

One approach, sometimes called the NIH Method because it was popularized by statisticians working at NIH, is to fit this model in two-stages:

- Fit a straight line (or curve) to the response data for each subject (stage 1), and then

- Regress the estimates of the individual intercepts and slopes on subject-specific covariates (stage 2).

One of the attractions of this method is that it was very easy to perform using existing statistical software for standard linear regression (i.e., before software like PROC MIXED).

This approach is nearly efficient when the dataset is balanced and complete.

It is somewhat less attractive when the number and timing of observations varies among subjects, because it does not take proper account of the different precisions among subjects in estimating their intercepts and slopes.

In contrast, we can consider the mixed effects model corresponding to the two-stage model, and obtain efficient (more precise) estimates of the regression coefficients <u>by fitting it all at once</u>.

We can combine the two components of the two-stage model:

$$\begin{aligned} Y_{ij} &= Z'_{ij}\beta_i + \epsilon_{ij} \\ &= Z'_{ij}(A_i\beta + b_i) + \epsilon_{ij} \\ &= (Z'_{ij}A_i)\beta + Z'_{ij}b_i + \epsilon_{ij} \\ &= X'_{ij}\beta + Z'_{ij}b_i + \epsilon_{ij}, \end{aligned}$$

where $X'_{ij} = Z'_{ij}A_i$.

$\Longrightarrow$ Linear Mixed Effects Model (albeit with constraint, $X'_{ij} = Z'_{ij}A_i$).

Mixed Effects Model Representation: Linear Trend

We can develop a mixed effects model in two stages corresponding to the two-stage model:

Stage 1:

$$Y_{ij} = \beta_{1i} + \beta_{2i}t_{ij} + \epsilon_{ij}$$

where β_{1i} and β_{2i} are the intercept and slope for the i^{th} subject,

and the errors, ϵ_{ij}, are assumed to be independent and normally distributed around the individual's regression line, i.e. $\epsilon_{ij} \sim N\left(0, \sigma^2\right)$.

Stage 2:

Assume that the intercept and slope, β_{1i} and β_{2i}, are random and have a joint multivariate normal distribution, with mean dependent on covariates:

$$\beta_{1i} = \beta_1 + \beta_2 \text{ Group } + b_{1i}$$

$$\beta_{2i} = \beta_3 + \beta_4 \text{ Group } + b_{2i}$$

Also, let $(b_{1i}) = g_{11}$, $(b_{1i}, b_{2i}) = g_{12}$, $(b_{2i}) = g_{22}$.

If we substitute the expressions for β_{1i} and β_{2i} into the equation in stage 1, we obtain

$$\begin{aligned} Y_{ij} &= \beta_1 + \beta_2 \text{ Group } + \beta_3 t_{ij} + \beta_4 \text{ Group } \times t_{ij} \\ &\qquad + b_{1i} + b_{2i} t_{ij} + \epsilon_{ij} \end{aligned}$$

The first four terms give the regression model for the mean response implied by the two-stage model (the fixed effect part of the model).

The last three terms are the random “error terms” (between- and within-subject).

LINEAR MIXED EFFECTS MODELS

Can develop a more general linear mixed effects model of the form:

$$Y_{ij} = X_{ij}'\beta + Z_{ij}'b_i + \epsilon_{ij},$$

Basic idea: Individuals in population are assumed to have their own subject-specific mean response trajectories over time.

Allow subset of the regression parameters to vary randomly from one individual to another, thereby accounting for sources of natural heterogeneity in the population.

Distinctive feature: mean response modelled as a combination of population characteristics (*fixed effects*) assumed to be shared by all individuals, and subject-specific effects (*random effects*) that are unique to a particular individual.

b_i is a $(q \times 1)$ vector of random effects and Z_{ij} is the vector of covariates linking the random effects to Y_{ij}.

Note: Components of Z_{ij} are a subset of the covariates in X_{ij}.

The random effects, b_i, are assumed to have a multivariate normal distribution with mean zero and covariance matrix denoted by G,

$$b_i \sim N(0, G).$$

For example, in the random intercepts and slopes model,

$$Y_{ij} = \beta_1 + \beta_2 t_{ij} + \beta_3 \mathrm{trt}_i + \beta_4 t_{ij} \times \mathrm{trt}_i + b_{1i} + b_{2i} t_{ij} + \epsilon_{ij},$$

G is a 2×2 matrix with unique components $g_{11} = \mathrm{Var}(b_{1i})$,
$g_{12} = \mathrm{Cov}(b_{1i}, b_{2i})$, and $g_{22} = \mathrm{Var}(b_{2i})$.

The within-subject errors, ϵ_{ij}, are assumed to have a multivariate normal distribution with mean zero and covariance matrix denoted by R_i,

$$\epsilon_i \sim N(0, R_i).$$

Note: Usually, it is assumed that $R_i = \sigma^2 I$, where I is a $(n_i \times n_i)$ identity matrix.

That is, when $R_i = \sigma^2 I$, the errors ϵ_{ij} within a subject are uncorrelated, with homogeneous variance.

$\Rightarrow$ "conditional independence assumption".

In principle, a structured model for R_i could be assumed, e.g., AR(1).

At the individual level, we have

$$Y_i = X_i\beta + Z_i b_i + \epsilon_i, \text{ where } X_i = Z_i A_i.$$

b_i and ϵ_i are (independent) random effects (between- and within-subject "errors")

There is an induced variance-covariance structure:

$$\text{Cov}(Y_i) = Z_i G Z_i' + \sigma^2 I_{n_i}.$$

In the simple model with random intercepts and slopes, this gives:

$$\begin{aligned} \text{Var}(Y_{ij}) &= g_{11} + 2t_{ij}g_{12} + t_{ij}^2 g_{22} + \sigma^2, \\ \text{Cov}(Y_{ij}, Y_{ik}) &= g_{11} + 2(t_{ij} + t_{ik})g_{12} + t_{ij}t_{ik}g_{22} \end{aligned}$$

Linear Models for the Mean Response

The mean response can be modelled by a familiar regression model.

For example, with a linear trend over time, we may have

$$E(Y_{ij}) = \mu_{ij} = \beta_1 + \beta_2 t_{ij}.$$

With additional covariates, this can be written more generally

$$E(Y_{ij}) = \beta_1 X_{ij1} + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp}$$

where t_{ij}, or possibly functions of t_{ij}, have been incorporated into the covariates, e.g., $X_{ij1} = 1$, $X_{ij2} = t_{ij}$, $X_{ij3} =$ treatment group indicator, and $X_{ij4} = t_{ij} \times$ treatment group indicator.

Model for Covariance: Random Intercept Model

One traditional approach for handling the covariance among repeated measures is to assume that it arises from a random subject effect.

That is, each subject is assumed to have an (unobserved) underlying level of response which persists across all of his/her repeated measurements.

This subject effect is treated as random and the model becomes

$$\begin{aligned} Y_{ij} &= \beta_1 X_{ij1} + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp} + b_i + \epsilon_{ij} \\ &= \beta_1 + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp} + b_i + \epsilon_{ij}, \end{aligned}$$

assuming $X_{ij1} = 1$ for all i and j, or

$$Y_{ij} = (\beta_1 + b_i) + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp} + \epsilon_{ij}$$

(also known as "random intercept model").

In the model

$$Y_{ij} = \beta_1 + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp} + b_i + \epsilon_{ij}$$

the response for the i^{th} subject at j^{th} occasion is assumed to differ from the population mean,

$$\mu_{ij} = E(Y_{ij}) = \beta_1 + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp}$$

by a subject effect, b_i, and a within-subject measurement error, ϵ_{ij}.

Furthermore, it is assumed that

$$b_i \sim N(0, \sigma_b^2); \qquad \epsilon_{ij} \sim N(0, \sigma^2)$$

and that b_i and ϵ_{ij} are mutually independent.
Note: Assumption of normality not always necessary.

Figure 1 provides graphical representation of the linear trend model:

$$Y_{ij} = (\beta_1 + b_i) + \beta_2 t_{ij} + \epsilon_{ij}$$

Overall mean response over time in the population changes linearly with time (denoted by the solid line).

Subject-specific mean responses for two specific individuals, subjects A and B, deviate from the population trend (denoted by the broken lines).

Individual A responds "higher" than the population average and thus has a positive b_i.

Individual B responds "lower" than the population average and has a negative b_i.

Inclusion of measurement errors, ϵ_{ij}, allows response at any occasion to vary randomly above/below subject-specific trajectories (see Figure 2).

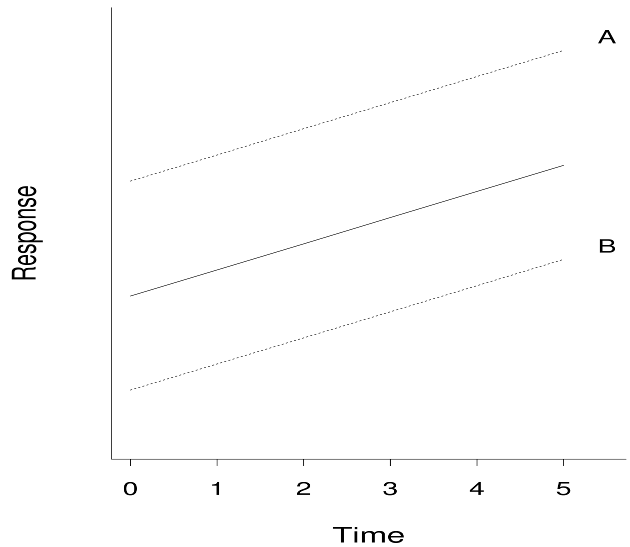

Figure 2: Graphical representation of the overall and subject-specific mean responses over time.

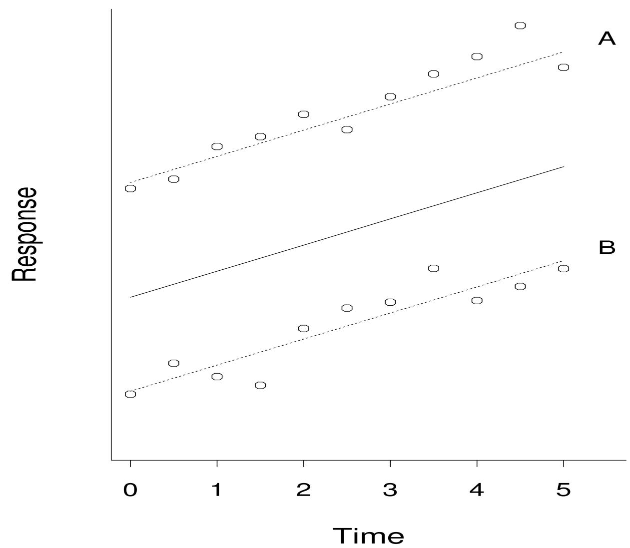

Figure 3: Graphical representation of the overall and subject-specific mean responses over time, plus measurement errors.

Covariance/Correlation Structure

Model: $Y_{ij} = \beta_1 + \beta_2 X_{ij2} + \cdots + \beta_p X_{ijp} + b_i + \epsilon_{ij}$
with $b_i \sim N(0, \sigma_b^2)$; $\epsilon_{ij} \sim N(0, \sigma^2)$ and b_i and ϵ_{ij} are mutually independent.

$$\text{Var}(Y_{ij}) = \text{Var}(b_j) + \text{Var}(\epsilon_{ij}) = \sigma_b^2 + \sigma^2$$

Note: The introduction of a random subject effect, b_i, induces correlation among the repeated measurements:

$$\text{Cov}(Y_{ij}, Y_{ik}) = \sigma_b^2 \Longrightarrow \text{Corr}(Y_{ij}, Y_{ik}) = \frac{\sigma_b^2}{\sigma_b^2 + \sigma^2}$$

This is the correlation among pairs of observations on the same individual.

Induced Covariance/Correlation Structure

The introduction of a random subject effect induces the simplest possible example of a mixed effect model, having a compound symmetry covariance structure:

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

Potential Drawback: Variances and correlations are assumed to be constant. across occasions.

Solution: Allow for heterogeneity in trends over time $\Longrightarrow$ random intercepts and slopes.

Extension: Random Intercept and Slope Model

Consider a model with intercepts and slopes that vary randomly among individuals,

$$Y_{ij} = \beta_1 + \beta_2 t_{ij} + b_{1i} + b_{2i} t_{ij} + \epsilon_{ij}, \quad j = 1, ..., n_i,$$

where t_{ij} denotes the timing of the j^{th} response on the i^{th} subject.

This model posits that individuals vary not only in their baseline level of response (when $t = 0$), but also in terms of their changes in the response over time (see Figure 3).

The effects of covariates (e.g., due to treatments, exposures) can be incorporated by allowing mean of intercepts and slopes to depend on covariates.

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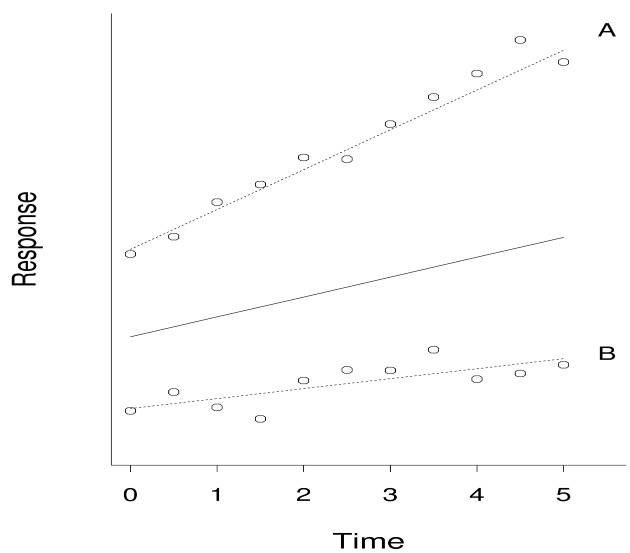

Figure 4: Graphical representation of the overall and subject-specific mean responses over time, plus measurement errors.

For example, consider two-group study comparing a *treatment* and a *control* group:

$$Y_{ij} = \beta_1 + \beta_2 t_{ij} + \beta_3 \text{trt}_i + \beta_4 t_{ij} \times \text{trt}_i + b_{1i} + b_{2i} t_{ij} + \epsilon_{ij},$$

where $\text{trt}_i = 1$ if the i^{th} individual assigned to treatment group, and $\text{trt}_i = 0$ otherwise.

The model can be re-expressed as follows for the *control* group and *treatment* group respectively:

trt = 0: $Y_{ij} = (\beta_1 + b_{1i}) + (\beta_2 + b_{2i}) t_{ij} + \epsilon_{ij},$

trt = 1: $Y_{ij} = (\beta_1 + \beta_3 + b_{1i}) + (\beta_2 + \beta_4 + b_{2i}) t_{ij} + \epsilon_{ij},$

Finally, consider the covariance induced by the introduction of random intercepts and slopes.

Assuming $b_{1i} \sim N(0, \sigma^2_{b_1})$, $b_{2i} \sim N(0, \sigma^2_{b_2})$ (with $\text{Cov}(b_{1i}, b_{2i}) = \sigma_{b_1,b_2}$) and $\epsilon_{ij} \sim N(0, \sigma^2)$, then

$$\begin{aligned} \text{Var}\left(Y_{ij}\right) &= \text{Var}\left(b_{1i} + b_{2i} t_{ij} + \epsilon_{ij}\right) \\ &= \text{Var}(b_{1i}) + 2t_{ij}\text{Cov}(b_{1i}, b_{2i}) + t^2_{ij}\text{Var}(b_{2i}) + \text{Var}(\epsilon_{ij}) \\ &= \sigma^2_{b_1} + 2t_{ij}\sigma_{b_1,b_2} + t^2_{ij}\sigma^2_{b_2} + \sigma^2. \end{aligned}$$

Similarly, it can be shown that

$$\text{Cov}\left(Y_{ij}, Y_{ik}\right) = \sigma^2_{b_1} + \left(t_{ij} + t_{ik}\right)\sigma_{b_1,b_2} + t_{ij} t_{ik} \sigma^2_{b_2}.$$

Thus, in this mixed effects model for longitudinal data the variances and correlations (covariance) are expressed as an explicit function of time, t_{ij}.

Conditional and Marginal Means

In the linear mixed effects model,

$$Y_{ij} = X_{ij}'\beta + Z_{ij}'b_i + \epsilon_{ij},$$

there is an important distinction between the conditional mean,

$$E(Y_{ij}|X_{ij}, b_i) = X_{ij}'\beta + Z_{ij}'b_i,$$

and the marginal mean,

$$E(Y_{ij}|X_{ij}) = X_{ij}'\beta.$$

The former describes the mean response for an individual, the latter describes the mean response averaged over individuals.

The distinction between the conditional and marginal means is best understood with a simple example.
Consider the simple random intercepts and slopes model,

$$Y_{ij} = \beta_1 + \beta_2 t_{ij} + b_{1i} + b_{2i}t_{ij} + \epsilon_{ij},$$

In this model, we can distinguish the conditional mean for an individual,

$$E(Y_{ij}|b_{1i}, b_{2i}) = \beta_1 + \beta_2 t_{ij} + b_{1i} + b_{2i}t_{ij},$$

(see broken lines for subjects A and B in Figure 4), and the marginal mean averaged over individuals,

$$E(Y_{ij}) = \beta_1 + \beta_2 t_{ij},$$

(see solid line in Figure 4).

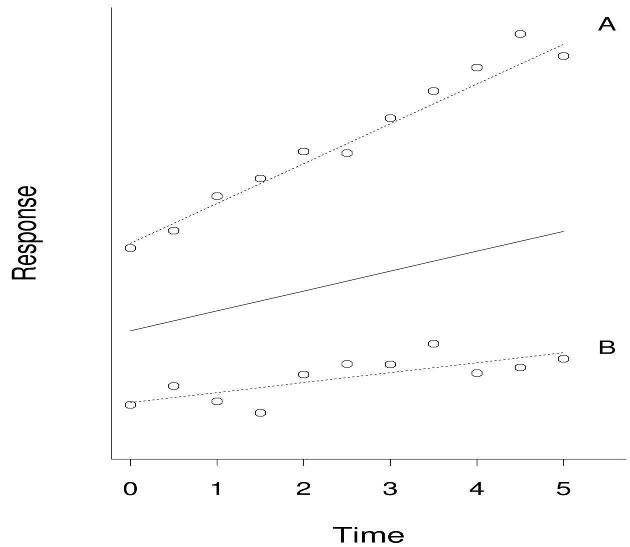

Figure 5: Graphical representation of the overall and subject-specific mean responses over time, plus measurement errors.

Conditional and Marginal Covariance

Variation and covariation can also be defined relative to the conditional and marginal means.

In the linear mixed effects model,

$$Y_{ij} = X_{ij}'\beta + Z_{ij}'b_i + \epsilon_{ij},$$

the conditional variance, $\mathrm{Var}(Y_{ij}|X_{ij}, b_i) = \mathrm{Var}(\epsilon_{ij}) = \sigma^2$ (when $R_i = \sigma^2 I$).

In contrast, the marginal covariance of the vector of responses Y_i is

$$\mathrm{Cov}(Y_i|X_i) = Z_i G Z_i' + R_i = Z_i G Z_i' + \sigma^2 I.$$

Note: This matrix has non-zero off-diagonal elements (i.e., introduction of random effects, b_i, induces correlation marginally among the Y_i).

The distinction between conditional and marginal (co)variances is best understood by considering the simple random intercepts and slopes model,

$$Y_{ij} = \beta_1 + \beta_2 t_{ij} + b_{1i} + b_{2i} t_{ij} + \epsilon_{ij}.$$

The conditional variance, $\mathrm{Var}(Y_{ij}|b_{1i}, b_{2i}) = \mathrm{Var}(\epsilon_{ij}) = \sigma^2$, describes variation in an individual's observations around her subject-specific mean (i.e., variation of observations around the broken line in Figure 5).

The marginal covariance describes (co)variation of the observations with respect to the marginal mean (i.e., variation and covariation of observations around the solid line in Figure 5):

$$\mathrm{Var}\,(Y_{ij}) = \sigma^2_{b_1} + 2t_{ij}\sigma_{b_1,b_2} + t^2_{ij}\sigma^2_{b_2} + \sigma^2.$$
$$\mathrm{Cov}\,(Y_{ij}, Y_{ik}) = \sigma^2_{b_1} + (t_{ij} + t_{ik})\,\sigma_{b_1,b_2} + t_{ij}t_{ik}\sigma^2_{b_2}.$$

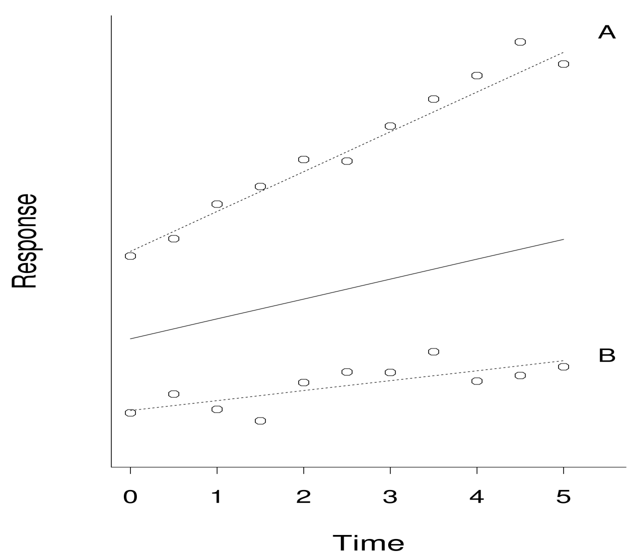

Figure 6: Graphical representation of the overall and subject-specific mean responses over time, plus measurement errors.

Estimation: Maximum Likelihood

ML estimator of $\beta_1, \beta_2, ..., \beta_p$ is the *generalized least squares* (GLS) estimator and depends on marginal covariance among the repeated measures (see Lecture 5).

In general, there is no simple expression for ML estimator of the covariance components - G and σ^2 (or R) - requires iterative techniques.

Because ML estimation of covariance is known to be biased in small samples, use *restricted* ML (REML) estimation instead.

Example: Exercise Therapy Trial

- Subjects were assigned to one of two weightlifting programs to increase muscle strength.
- Treatment 1: number of repetitions of the exercises was increased as subjects became stronger.
- Treatment 2, number of repetitions was held constant but amount of weight was increased as subjects became stronger.
- Measurements of body strength were taken at baseline and on days 2, 4, 6, 8, 10, and 12.
- We focus only on measures of strength obtained at baseline (or day 0) and on days 4, 6, 8, and 12.

Example: Exercise Therapy Trial

Consider a model with intercepts and slopes that vary randomly among subjects, and which allows the mean values of the intercept and slope to differ in the two treatment groups.

To fit this model, use the following code:

```
PROC MIXED DATA = stren;
      CLASS id trt;
      MODEL y=trt time time*trt / S CHISQ;
      RANDOM INTERCEPT time / TYPE=UN SUBJECT=ID G;
```


Selected Output from PROC MIXED

Estimated G Matrix

Effect	id	col1	col2
Intercept	1	9.5469	0.05331
time	1	0.0533	0.02665

Residual: 0.6862

Fit Statistics

-2 Res Log Likelihood	632.0
AIC (smaller is better)	640.0
AICC (smaller is better)	640.2
BIC (smaller is better)	646.4

Solution for Fixed Effects

Effect	trt	Estimate	Standard Error	DF	t Value	Pr > $\|t\|$
Intercept		81.2396	0.6910	35	117.57	<.0001
trt	1	-1.2349	1.0500	99	-1.18	0.2424
trt	2	0	.	.	.	.
time		0.1729	0.0427	35	4.05	0.0003
time*trt	1	-0.0377	0.0637	99	-0.59	0.5548
time*trt	2	0	.	.	.	.

Recall:

$$\begin{aligned}\mathrm{Cov}(Y_i) &= Z_i G Z_i' + R_i \\ &= Z_i G Z_i' + \sigma^2 I\end{aligned}$$

Given estimates of G:

$$\begin{bmatrix} 9.54695 & 0.05331 \\ 0.05331 & 0.02665 \end{bmatrix}$$

and of $R_i = \sigma^2 I = (0.6862)I$,

and with

$$Z_i = \begin{bmatrix} 1 & 0 \\ 1 & 4 \\ 1 & 6 \\ 1 & 8 \\ 1 & 12 \end{bmatrix}$$

We can obtain the following estimate of $\text{Cov}\,(Y_i)$:

$$\begin{bmatrix} 10.23 & 9.76 & 9.87 & 9.97 & 10.19 \\ 9.76 & 11.09 & 10.72 & 11.04 & 11.68 \\ 9.87 & 10.72 & 11.83 & 11.57 & 12.43 \\ 9.97 & 11.04 & 11.57 & 12.79 & 13.17 \\ 10.19 & 11.68 & 12.43 & 13.17 & 15.35 \end{bmatrix}$$

The corresponding correlation matrix is:

$$\begin{bmatrix} 1.000 & 0.916 & 0.897 & 0.872 & 0.813 \\ 0.916 & 1.000 & 0.936 & 0.927 & 0.895 \\ 0.897 & 0.936 & 1.000 & 0.941 & 0.922 \\ 0.872 & 0.927 & 0.941 & 1.000 & 0.940 \\ 0.813 & 0.895 & 0.922 & 0.940 & 1.000 \end{bmatrix}$$

These can be obtained using the following options in PROC MIXED:
RANDOM INTERCEPT time / TYPE=UN SUBJECT=id G V VCORR;