REPEATED MEASURES

Repeated Measures Example

In an exercise therapy study, subjects were assigned to one of three weightlifting programs

i=1: The number of repetitions of weightlifting was increased as subjects became stronger (RI).

i=2: The amount of weight was increased as subjects became stronger (WI).

i=3: Subjects did not participate in weightlifting (XCont).

- Measurements of strength (y) were taken on days 2, 4, 6, 8, 10, 12 and 14 for each subject.
- Source: Littel, Freund, and Spector (1991), SAS System for Linear Models.
- R code: RepeatedMeasures.R

A Linear Mixed-Effect Model

$$y_{ijk} = \mu + \alpha_i + s_{ij} + \tau_k + \gamma_{ik} + e_{ijk}$$

Y_{ijk} strength measurement for program i, subject j, time point k

α_i fixed program effect

s_{ij} random subject effect

τ_k fixed time effect

γ_{ik} fixed program$\times$time interaction

e_{ijk} random error

Initially, we will assume

$$s_{ij} \overset{i.i.d.}{\sim} N(0, \sigma_s^2) \text{ independent of } e_{ijk} \overset{i.i.d.}{\sim} N(0, \sigma_e^2).$$

Average strength after $2k$ days on the ith program is

$$
\begin{aligned}
\mu_{ik} &= E(y_{ijk}) \\
&= E(\mu + \alpha_i + s_{ij} + \tau_k + \gamma_{ik} + e_{ijk}) \\
&= \mu + \alpha_i + E(s_{ij}) + \tau_k + \gamma_{ik} + E(e_{ijk}) \\
&= \mu + \alpha_i + \tau_k + \gamma_{ik}
\end{aligned}
$$

for $i = 1, 2, 3$ and $k = 1, 2, \ldots, 7$.

The variance of any single observation is

$$\begin{aligned}
\mathrm{Var}(y_{ijk}) &= \mathrm{Var}(\mu + \alpha_i + s_{ij} + \tau_k + \gamma_{ik} + e_{ijk}) \\
&= \mathrm{Var}(s_{ij} + e_{ijk}) \\
&= \mathrm{Var}(s_{ij}) + \mathrm{Var}(e_{ijk}) \\
&= \sigma_s^2 + \sigma_e^2.
\end{aligned}$$

The covariance between an two different observations from the same subject is

$$\begin{aligned}
\mathrm{Cov}(y_{ijk}, y_{ij\ell}) &= \mathrm{Cov}(\mu + \alpha_i + s_{ij} + \tau_k + \gamma_{ik} + e_{ijk}, \\
&\qquad \mu + \alpha_i + s_{ij} + \tau_\ell + \gamma_{i\ell} + e_{ij\ell}) \\
&= \mathrm{Cov}(s_{ij} + e_{ijk}, s_{ij} + e_{ij\ell}) \\
&= \mathrm{Cov}(s_{ij}, s_{ij}) + \mathrm{Cov}(s_{ij}, e_{ij\ell}) \\
&\quad + \mathrm{Cov}(e_{ijk}, s_{ij}) + \mathrm{Cov}(e_{ijk}, e_{ij\ell}) \\
&= \mathrm{Var}(s_{ij}) = \sigma_s^2.
\end{aligned}$$

The correlation between y_{ijk} and $y_{ij\ell}$ is

$$\frac{\sigma_s^2}{\sigma_s^2 + \sigma_e^2} \equiv \rho.$$

Observations taken on different subjects are uncorrelated.

For the set of observations taken on a single subject, we have

$$\text{Var}\left(\begin{bmatrix} y_{ij1} \\ y_{ij3} \\ \vdots \\ y_{ij7} \end{bmatrix}\right) = \begin{bmatrix} \sigma_e^2 + \sigma_s^2 & \sigma_s^2 & \cdots & \sigma_s^2 \\ \sigma_s^2 & \sigma_e^2 + \sigma_s^2 & \cdots & \sigma_s^2 \\ \vdots & \vdots & \ddots & \sigma_s^2 \\ \sigma_s^2 & \sigma_s^2 & \sigma_s^2 & \sigma_e^2 + \sigma_s^2 \end{bmatrix}$$

$$= \sigma_e^2 \boldsymbol{I}_{7\times 7} + \sigma_s^2 \mathbf{1}\mathbf{1}'_{7\times 7}.$$

This is known as a *compound symmetric* covariance structure.

Using n_i to denote the number of subjects in the ith program, we can write this model in the form

$$\boldsymbol{y} = \boldsymbol{X\beta} + \mathbf{Zu} + \mathbf{e}$$

as follows.

$$
\begin{bmatrix} y_{111} \\ y_{112} \\ \vdots \\ y_{117} \\ y_{121} \\ y_{122} \\ \vdots \\ y_{127} \\ \vdots \\ y_{211} \\ y_{212} \\ \vdots \\ y_{217} \\ \vdots \\ y_{3n_31} \\ y_{3n_32} \\ \vdots \\ y_{3n_37} \end{bmatrix}
=
\left[\begin{array}{cccc|c|c}
1 & 1 & 0 & 0 & 1000000 & 21 \\
1 & 1 & 0 & 0 & 0100000 & \text{columns} \\
 & \vdots & & & \ddots & \text{for} \\
1 & 1 & 0 & 0 & 0000001 & \text{interaction} \\
1 & 1 & 0 & 0 & 1000000 & \\
1 & 1 & 0 & 0 & 0100000 & \\
 & \vdots & & & \ddots & \\
1 & 1 & 0 & 0 & 0000001 & \\
\vdots & & & & & \\
1 & 0 & 1 & 0 & 1000000 & \\
1 & 0 & 1 & 0 & 0100000 & \\
 & & \vdots & & \ddots & \\
1 & 0 & 1 & 0 & 0000001 & \\
\vdots & & & & & \\
1 & 0 & 0 & 1 & 1000000 & \\
1 & 0 & 0 & 1 & 0100000 & \\
\vdots & & \vdots & & \ddots & \\
1 & 0 & 0 & 1 & 0000001 &
\end{array}\right]
\begin{bmatrix} \mu \\ \alpha_1 \\ \alpha_2 \\ \alpha_3 \\ \tau_1 \\ \tau_2 \\ \tau_3 \\ \tau_4 \\ \tau_5 \\ \tau_6 \\ \tau_7 \\ \gamma_{11} \\ \gamma_{12} \\ \vdots \\ \gamma_{37} \end{bmatrix}
+
$$

$$
\begin{bmatrix}
1 & 0 & \cdots & 0 \\
1 & 0 & \cdots & 0 \\
\vdots & \vdots & & \vdots \\
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & & \vdots \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & & \vdots \\
\vdots & \vdots & & \vdots \\
\vdots & \vdots & & \vdots \\
0 & 0 & \cdots & 1 \\
0 & 0 & \cdots & 1 \\
\vdots & \vdots & & \vdots \\
0 & 0 & \cdots & 1
\end{bmatrix}
\begin{bmatrix}
s_{11} \\ s_{12} \\ \vdots \\ \vdots \\ \vdots \\ s_{3n_3}
\end{bmatrix}
+
\begin{bmatrix}
e_{111} \\ e_{112} \\ \vdots \\ e_{117} \\ e_{121} \\ e_{122} \\ \vdots \\ e_{127} \\ \vdots \\ \vdots \\ \vdots \\ e_{3n_31} \\ e_{3n_32} \\ \vdots \\ e_{3n_37}
\end{bmatrix}
$$

In this case,

$$\boldsymbol{G} = \text{Var}(\mathbf{u}) \;=\; \sigma_s^2 \boldsymbol{I}_{m\times m} \text{ and}$$

$$\boldsymbol{R} = \text{Var}(\mathbf{e}) \;=\; \sigma_e^2 \boldsymbol{I}_{(7m)\times(7m)},$$

where $m = n_1 + n_2 + n_3$ is the total number of subjects.

$$\boldsymbol{\Sigma} = \text{Var}(\boldsymbol{y}) \;=\; \boldsymbol{ZGZ}' + \boldsymbol{R}$$

is a block diagonal matrix with one block of the form

$$\sigma_s^2 \mathbf{11}'_{7\times 7} + \sigma_e^2 \boldsymbol{I}_{7\times 7}$$

for each subject.

LSMEAN for Program i and Time k

$$\bar{y}_{i \cdot k} = \frac{1}{n_i} \sum_{j=1}^{n_i} y_{ijk} = \mu + \alpha_i + \bar{s}_{i \cdot} + \tau_k + \gamma_{ik} + \bar{e}_{i \cdot k}$$

$$\text{Var}(\bar{y}_{i \cdot k}) = \frac{\sigma_s^2 + \sigma_e^2}{n_i}$$

$$\text{se} = \sqrt{\left(\frac{6}{7} MS_{\text{error}} + \frac{1}{7} MS_{\text{subj(prog)}}\right) \frac{1}{n_i}}$$

Cochran-Satterthwaite degrees of freedom = 65.8.

LSMEAN for Program i

$$\frac{1}{7}\sum_{k=1}^{7}\bar{y}_{i\cdot k} = \bar{y}_{i\cdot\cdot} = \mu + \alpha_i + \bar{s}_{i\cdot} + \bar{\tau}_{\cdot} + \bar{\gamma}_{i\cdot} + \bar{e}_{i\cdot\cdot}$$

$$\text{Var}(\bar{y}_{i\cdot\cdot}) = \frac{7\sigma_s^2 + \sigma_e^2}{7n_i}$$

$$\text{se} = \sqrt{\frac{MS_{\text{subj(prog)}}}{7n_i}}$$

Degrees of freedom = 54 because there are $n_1 = 16,\ n_2 = 21,\ n_3 = 20$ subjects in the three programs.

LSMEAN for time k

$$\frac{1}{3}\sum_{i=1}^{3}\bar{y}_{i\cdot k} = \mu + \bar{\alpha}_{.} + \frac{1}{3}\sum_{i=1}^{3}\bar{s}_{i.} + \tau_k + \bar{\gamma}_{\cdot k} + \frac{1}{3}\sum_{i=1}^{3}\bar{e}_{i\cdot k}$$

$$\text{Var}\left(\frac{1}{3}\sum_{i=1}^{3}\bar{y}_{i\cdot k}\right) = \frac{1}{9}\sum_{i=1}^{3}\frac{\sigma_e^2 + \sigma_s^2}{n_i}$$

$$\text{se} = \frac{1}{3}\sqrt{\left(\frac{6}{7}MS_{\text{error}} + \frac{1}{7}MS_{\text{subj(prog)}}\right)\left(\sum_{i=1}^{3}\frac{1}{n_i}\right)}$$

Cochran-Satterthwaite degrees of freedom = 65.8.

Difference between Strength Means at Times k and ℓ (Averaging across Programs)

$$\begin{aligned}
\frac{1}{3}\sum_{i=1}^{3}(\bar{y}_{i\cdot k} - \bar{y}_{i\cdot \ell}) &= \frac{1}{3}\sum_{i=1}^{3}\frac{1}{n_i}\sum_{j=1}^{n_i}(y_{ijk} - y_{ij\ell}) \\
&= \tau_k - \tau_\ell + \bar{\gamma}_{\cdot k} - \bar{\gamma}_{\cdot \ell} \\
&\quad + \frac{1}{3}\sum_{i=1}^{3}\frac{1}{n_i}\sum_{j=1}^{n_i}(e_{ijk} - e_{ij\ell})
\end{aligned}$$

Note that subject effects cancel out.

The variance of the estimator is

$$\frac{2\sigma_e^2}{9}\sum_{i=1}^{3}\frac{1}{n_i}.$$

Thus, the standard error of the estimator is

$$\sqrt{\frac{2MS_{\text{error}}}{9}\sum_{i=1}^{3}\frac{1}{n_i}}.$$

Degrees of freedom

$= 7(16+21+20)-(1+2+54+6+12) = 324.$

Difference between Strength Means for Program i and ℓ at Time k

$$\bar{y}_{i\cdot k} - \bar{y}_{\ell\cdot k} = \alpha_i - \alpha_\ell + \gamma_{ik} - \gamma_{\ell k} + \bar{s}_{i\cdot} - \bar{s}_{\ell\cdot} + \bar{e}_{i\cdot k} - \bar{e}_{\ell\cdot k}$$

$$\mathrm{Var}(\bar{y}_{i\cdot k} - \bar{y}_{\ell\cdot k}) = (\sigma_e^2 + \sigma_s^2)\left(\frac{1}{n_i} + \frac{1}{n_\ell}\right)$$

$$\mathrm{se} = \sqrt{\left(\frac{6}{7}MS_{\mathrm{error}} + \frac{1}{7}MS_{\mathrm{subj(prog)}}\right)\left(\frac{1}{n_i} + \frac{1}{n_\ell}\right)}$$

Cochran-Satterthwaite degrees of freedom $= 65.8$.

Difference between Strength Means at Times k and ℓ within a Program i

$$\bar{y}_{i\cdot k} - \bar{y}_{i\cdot \ell} = \tau_k - \tau_\ell + \gamma_{ik} - \gamma_{i\ell} + \bar{e}_{i\cdot k} - \bar{e}_{i\cdot \ell}$$

$$\mathrm{Var}(\bar{y}_{i\cdot k} - \bar{y}_{i\cdot \ell}) = \mathrm{Var}\left(\frac{1}{n_i}\sum_{j=1}^{n_i}(y_{ijk} - y_{ij\ell})\right) = \frac{2\sigma_e^2}{n_i}$$

$$\mathrm{se} = \sqrt{MS_{\mathrm{error}}\left(\frac{2}{n_i}\right)}$$

Degrees of freedom = 324.

Difference in Strength Means between Programs i and ℓ (Averaging across Time)

$$\bar{y}_{i\cdot\cdot} - \bar{y}_{\ell\cdot\cdot} = \alpha_i - \alpha_\ell + \bar{\gamma}_{i\cdot} - \bar{\gamma}_{\ell\cdot} + \bar{s}_{i\cdot} - \bar{s}_{\ell\cdot} + \bar{e}_{i\cdot\cdot} - \bar{e}_{\ell\cdot\cdot}$$

$$\text{Var}(\bar{y}_{i\cdot\cdot} - \bar{y}_{\ell\cdot\cdot}) = (7\sigma_s^2 + \sigma_e^2)\left(\frac{1}{7n_i} + \frac{1}{7n_\ell}\right)$$

$$\text{se} = \sqrt{MS_{\text{subj(prog)}}\left(\frac{1}{7n_i} + \frac{1}{7n_\ell}\right)}$$

Degrees of freedom = 54.

Other Variance Matrices

We began with the model

$$y_{ijk} = \mu + \alpha_i + s_{ij} + \tau_k + \gamma_{ik} + e_{ijk}$$

where

$$s_{ij} \overset{i.i.d.}{\sim} N(0, \sigma_s^2) \text{ independent of } e_{ijk} \overset{i.i.d.}{\sim} N(0, \sigma_e^2).$$

This model was expressed in the form

$$\boldsymbol{y} = \boldsymbol{X\beta} + \mathbf{Zu} + \mathbf{e},$$

where

$$\mathbf{u} = \begin{bmatrix} s_{11} \\ \vdots \\ s_{3n_3} \end{bmatrix}$$

contained the random subject effects.

Here

$$\boldsymbol{G} = \text{Var}(\mathbf{u}) = \sigma_s^2 \boldsymbol{I},\ \boldsymbol{R} = \text{Var}(\mathbf{e}) = \sigma_e^2 \boldsymbol{I},\ \text{and}$$

$$\begin{aligned}
\boldsymbol{\Sigma} &= \text{Var}(\boldsymbol{y}) = \boldsymbol{ZGZ}' + \boldsymbol{R} \\
&= \sigma_s^2 \begin{bmatrix} \mathbf{11}' & & & \\ & \mathbf{11}' & & \\ & & \ddots & \\ & & & \mathbf{11}' \end{bmatrix} + \sigma_e^2 \boldsymbol{I} \\
&= \begin{bmatrix} \sigma_e^2 \boldsymbol{I} + \sigma_s^2 \mathbf{11}' & & \\ & \ddots & \\ & & \sigma_e^2 \boldsymbol{I} + \sigma_s^2 \mathbf{11}' \end{bmatrix}.
\end{aligned}$$

If you are not interested in predicting subject effects (random subject effects are included only to introduce correlation among repeated measures on the same subject), you can work with an alternative expression of the same model by using the general linear model $\boldsymbol{y} = \boldsymbol{X\beta} + \boldsymbol{\epsilon}$, where

$$\text{Var}(\boldsymbol{y}) = \text{Var}(\boldsymbol{\epsilon}) = \begin{bmatrix} \sigma_e^2 \boldsymbol{I} + \sigma_s^2 \mathbf{1}\mathbf{1}' & & \\ & \ddots & \\ & & \sigma_e^2 \boldsymbol{I} + \sigma_s^2 \mathbf{1}\mathbf{1}' \end{bmatrix}.$$

More generally, we can replace the mixed model

$$\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \mathbf{Z}\mathbf{u} + \mathbf{e}$$

with the model

$$\boldsymbol{y} = \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\epsilon}$$

where

$$\mathrm{Var}(\boldsymbol{y}) = \mathrm{Var}(\boldsymbol{\epsilon}) = \begin{bmatrix} \boldsymbol{W} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{W} & \cdots & \mathbf{0} \\ \vdots & \vdots & \ddots & \vdots \\ \mathbf{0} & \mathbf{0} & \cdots & \boldsymbol{W} \end{bmatrix}.$$

- We can choose a structure for $\boldsymbol{W}$ that seems appropriate based on the design and the data.

- One choice for $\boldsymbol{W}$ is a compound symmetric matrix like we have considered previously.

- Another choice for $\boldsymbol{W}$ is an unstructured positive definite matrix.

- A common choice for $\boldsymbol{W}$ when repeated measures are equally spaced in time is the first order autoregressive structure known as AR(1).

AR(1):First Order Autoregressive Covariance Structure

$$\boldsymbol{W} = \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 & \rho^4 & \rho^5 & \rho^6 \\ \rho & 1 & \rho & \rho^2 & \rho^3 & \rho^4 & \rho^5 \\ \rho^2 & \rho & 1 & \rho & \rho^2 & \rho^3 & \rho^4 \\ \rho^3 & \rho^2 & \rho & 1 & \rho & \rho^2 & \rho^3 \\ \rho^4 & \rho^3 & \rho^2 & \rho & 1 & \rho & \rho^2 \\ \rho^5 & \rho^4 & \rho^3 & \rho^2 & \rho & 1 & \rho \\ \rho^6 & \rho^5 & \rho^4 & \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

where $\sigma^2 \in (0, \infty)$ and $\rho \in (-1, 1)$ are unknown parameters.