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:**

**R code:** RepeatedMeasures.R
Mixed model

\[ Y_{ijk} = \mu + \alpha_i + S_{ij} + \tau_k + \gamma_{ik} + e_{ijk} \]

\(Y_{ijk}\) strength measurement for

prog. \(i\), subj. \(j\), time point \(k\)

\(\alpha_i\) fixed program effect

\(S_{ij}\) random subject effect

\(\tau_k\) fixed time effect

\(\gamma_{ik}\) fixed prog. \(\times\) time interaction

\(e_{ijk}\) random error

where the random effects are all independent and

\[ S_{ij} \sim NID(0, \sigma^2_S) \]
\[ e_{ijk} \sim NID(0, \sigma^2_\epsilon) \]
Average strength after $2k$ days on the $i$-th program is

$$\mu_{ik} = E(Y_{ijk})$$
$$= E(\mu + \alpha_i + S_{ij} + \tau_k + \gamma_{ik} + e_{ijk})$$
$$= \mu + \alpha_i + E(S_{ij}) + \tau_k + \gamma_{ik} + E(e_{ijk})$$
$$= \mu + \alpha_i + \tau_k + \gamma_{ik}$$

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

The variance of any single observation is

$$Var(Y_{ijk}) = Var(\mu + \alpha_i + S_{ij} + \tau_k + \alpha_{ik} + e_{ijk})$$
$$= Var(S_{ij} + e_{ijk})$$
$$= Var(S_{ij}) + Var(e_{ijk})$$
$$= \sigma_S^2 + \sigma_e^2$$
Correlation between observations taken on the same subject:

\[ \text{Cov}(Y_{ijk}, Y_{ij\ell}) \]

\[ = \text{Cov}(\mu + \alpha_i + S_{ij} + \tau_k + \gamma_{ik} + e_{ijk}, \]

\[ \mu + \alpha_i + S_{ij} + \tau_{\ell} + \gamma_{i\ell} + e_{ij\ell}) \]

\[ = \text{Cov}(S_{ij} + e_{ijk}, S_{ij} + e_{ij\ell}) \]

\[ = \text{Cov}(S_{ij}, S_{ij}) + \text{Cov}(S_{ij}, e_{ij\ell}) \]

\[ + \text{Cov}(e_{ijk}, S_{ij}) + \text{Cov}(e_{ijk}, e_{ij\ell}) \]

\[ = \text{Var}(S_{ij}) \quad \text{for } k \neq \ell \]

\[ = \sigma_S^2. \]
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

\[
Var \left( \begin{bmatrix}
Y_{ij1} \\
Y_{ij3} \\
\vdots \\
Y_{ij7}
\end{bmatrix} \right) = \begin{bmatrix}
\sigma_e^2 + \sigma_S^2 & \sigma_S^2 & \cdots & \sigma_S^2 \\
\sigma_S^2 & \sigma_e^2 + \sigma_S^2 & \cdots & \sigma_S^2 \\
\vdots & \vdots & \ddots & \vdots \\
\sigma_S^2 & \sigma_S^2 & \sigma_S^2 & \sigma_e^2 + \sigma_S^2
\end{bmatrix} = \sigma_e^2 I + \sigma_S^2 J
\]

\[J\] is a matrix of ones

This covariance structure is called compound symmetry.
Write this model in the form

\[ Y = X\beta + Zu + e \]

\[
\begin{bmatrix}
Y_{111} & Y_{112} & \vdots & Y_{117} & Y_{121} & Y_{122} & \vdots & Y_{127} & \vdots & Y_{211} & Y_{212} & \vdots & Y_{217} & \vdots & Y_{3,n_31} & Y_{3,n_32} & \vdots & Y_{3,n_37}
\end{bmatrix}
\begin{bmatrix}
1 & 1 & 0 & 0 & 1000000 & 1000000 & 0000001 & 1000000 & 0100000 & 0100000 & 0000001 & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots
\end{bmatrix}
\begin{bmatrix}
\mu \\
\alpha_1 \\
\alpha_2 \\
\alpha_3 \\
\tau_1 \\
\tau_2 \\
\tau_3 \\
\tau_4 \\
\tau_5 \\
\tau_6 \\
\tau_7 \\
\gamma_{11} \\
\gamma_{12} \\
\vdots \\
\gamma_{37}
\end{bmatrix}
\]
\[
\begin{pmatrix}
1 & 0 & \cdots & 0 \\
1 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
1 & 0 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 1 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1 \\
0 & 0 & \cdots & 1 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & 1 \\
\end{pmatrix} + \begin{pmatrix}
S_{11} \\
S_{12} \\
\vdots \\
S_{3,n_3} \\
\end{pmatrix} + \begin{pmatrix}
e_{111} \\
e_{112} \\
\vdots \\
e_{117} \\
e_{121} \\
e_{122} \\
\vdots \\
e_{127} \\
e_{211} \\
e_{212} \\
\vdots \\
e_{217} \\
e_{3,n_31} \\
e_{3,n_32} \\
\vdots \\
e_{3,n_37} \\
\end{pmatrix}
\]
In this case:

\[ R = \text{Var}(e) = \sigma^2_e I_{(7r) \times (7r)} \]

\[ G = \text{Var}(u) = \sigma^2_S I_{r \times r} \]

where \( r \) is the number of subjects

\[ \Sigma = \text{Var}(Y) = ZGZ^T + R \]

is a block diagonal matrix with one block of the form

\[ (\sigma^2_e I_{7 \times 7} + \sigma^2_S J_{7 \times 7}) \]

for each subject
Mean strength at a particular time in a particular program

\[ \text{LSMEAN} = \hat{\mu} + \hat{\alpha}_i + \hat{\tau}_k + \hat{\gamma}_{ik} \]

\[ = \bar{Y}_{i.k} = \frac{1}{n_i} \sum_{j=1}^{n_i} Y_{ijk} \]

\[ \text{Var}(\bar{Y}_{i.k}) = \frac{\sigma^2_e + \sigma^2_S}{n_i} \]

\[ S_{\bar{Y}_{i.k}} = \sqrt{\left( \frac{6}{7} MS_{error} + \frac{1}{7} MS_{Subj} \right) \frac{1}{n_i}} \]

\[ \uparrow \]

Cochran-Satterthwaite degrees of freedom are 65.8
Program means  
(averaging across time)

\( \text{LSMEAN} = \bar{Y}_{i..} \)

\[ = \hat{\mu} + \hat{\alpha}_i + \frac{1}{7} \sum_{k=1}^{7} (\hat{\tau}_k + \hat{\gamma}_{ik}) \]

\( \text{Var}(\bar{Y}_{i..}) = \frac{\sigma_e^2 + 7\sigma_S^2}{7n_i} \)

\( S_{\bar{Y}_{i..}} = \sqrt{\frac{MS_{\text{subjects}}}{2n_i}} \)

There are \( n_1 = 16 \), \( n_2 = 21 \), \( n_3 = 20 \) subjects in the three programs.
Mean strength at a particular time point (averaging across programs)

\[ LSMEAN = \hat{\mu} + \hat{\tau}_k + \frac{1}{3} \sum_{i=1}^{3} (\hat{\alpha}_i + \hat{\gamma}_{ik}) \]

\[ = \frac{1}{3} \sum_{i=1}^{3} (\bar{Y}_{i.k}) \neq \bar{Y}_{..k} \]

because \( n_1 = 16, n_2 = 21, n_3 = 20. \)

\[ \text{Var}(LSMEAN) = \frac{1}{9} \sum_{i=1}^{3} \frac{\sigma^2_e + \sigma^2_S}{n_i} \]

\[ S_{LSMEAN} = \frac{1}{3} \sqrt{\left(\frac{6}{7} MS_{error} + \frac{1}{7} MS_{subj}\right) \left(\sum_{i=1}^{3} \frac{1}{n_i}\right)} \]

↑

Cochran-Satterthwaite degrees of freedom are 65.8
Difference between strength means at two time points (averaging across programs)

\[
(\hat{\tau}_k + \frac{1}{3} \sum_{i=1}^{3} \hat{\gamma}_{ik}) - (\hat{\tau}_\ell - \frac{1}{3} \sum_{i=1}^{3} \hat{\gamma}_{i\ell})
\]

\[
= \frac{1}{3} \left( \sum_{i=1}^{3} \bar{Y}_{i.k} \right) - \frac{1}{3} \left( \sum_{i=1}^{3} \bar{Y}_{i.\ell} \right)
\]

\[
= \frac{1}{3} \sum_{i=1}^{3} \frac{1}{n_i} \sum_{j=1}^{n_i} (Y_{ijk} - Y_{ij\ell})
\]

↑

subject effects cancel out
Variance formula:

\[ \frac{2\sigma^2}{9} \sum_{i=1}^{3} \frac{1}{n_i} \]

Standard error:

\[ \sqrt{\frac{2MS_{\text{error}}}{9} \sum_{i=1}^{3} \frac{1}{n_i}} = 0.206 \]

↑

use degrees of freedom for error = 324
Difference between strength means for two programs at a specific time point

\[(\hat{\mu} + \hat{\alpha}_i + \hat{\tau}_{ik} + \hat{\gamma}_{ik}) - (\hat{\mu} + \hat{\alpha}_\ell + \hat{\tau}_k + \hat{\gamma}_{\ell k})\]

\[= \bar{Y}_{i,k} - \bar{Y}_{\ell,k}\]

\[\text{Var}(\bar{Y}_{i,k} - \bar{Y}_{\ell,k}) = (\sigma^2_e + \sigma^2_S)\left(\frac{1}{n_i} + \frac{1}{n_\ell}\right)\]

\[S_{\bar{Y}_{i,k} - \bar{Y}_{\ell,k}} = \sqrt{\left(\frac{6}{7}MS_{error} + \frac{1}{7}MS_{subj}\right)\left(\frac{1}{n_i} + \frac{1}{n_\ell}\right)}\]

↑

Use Cochran-Satterthwaite degrees of freedom = 65.8
Difference between strength means at two time points within a particular program

\[(\hat{\mu} + \hat{\alpha}_i + \hat{\tau}_k + \hat{\gamma}_{ik}) - (\hat{\mu} + \hat{\alpha}_i + \hat{\tau}_\ell + \hat{\gamma}_{i\ell})\]

\[= \bar{Y}_{i.k} - \bar{Y}_{i.\ell}\]

\[V ar(\bar{Y}_{i.k} - \bar{Y}_{i.\ell}) = \]

\[V ar\left(\frac{1}{n_i} \sum_{j=1}^{n_i} (Y_{ijk} - Y_{ij\ell})\right) = \frac{2\sigma_e^2}{n_i}\]

\[S_{\bar{Y}_{i.k} - \bar{Y}_{i.\ell}} = \sqrt{M S_{\text{error}} \left(\frac{2}{n_i}\right)}\]

\[\uparrow\]

use degrees of freedom for error=324
Difference in strength means for two programs (averaging across time points)

\[
\bar{Y}_{i..} - \bar{Y}_{\ell..} = (\hat{\alpha}_i - \frac{1}{7} \sum_{k=1}^{7} \hat{\gamma}_{ik}) - (\hat{\alpha}_\ell + \frac{1}{7} \sum_{k=1}^{7} \hat{\gamma}_{\ell k})
\]

\[
\text{Var}(\bar{Y}_{i..} - \bar{Y}_{\ell..}) = (\sigma^2_e + 7\sigma^2_S)(\frac{1}{7n_i} + \frac{1}{7n_\ell})
\]

\[
S_{\bar{Y}_{i..} - \bar{Y}_{\ell..}} = \sqrt{\frac{M S_{\text{subjects}}}{n_i} + \frac{1}{7n_\ell}}
\]

\[\uparrow \quad 54 \text{ d.f.}\]
Specifying other covariance matrices

We began with the model

\[ Y_{ijk} = \mu + \alpha_i + S_{ij} + \tau_k + \gamma_{ik} + e_{ijk} \]

where

\[ S_{ij} \sim NID(0, \sigma^2_S) \]

\[ e_{ijk} \sim NID(0, \sigma^2_e) \]

and the \( \{S_{ij}\} \) are distributed independently of the \( \{e_{ijk}\} \)
This model was expressed in the form

\[ Y = X\beta + Zu + e \]

where

\[ u = \begin{bmatrix} S_{11} \\ \vdots \\ S_{3,20} \end{bmatrix} \]

contained the random subject effects
Here

\[ G = \text{Var}(u) = \sigma_S^2 I \]

\[ R = \text{Var}(e) = \sigma_e^2 I \]

\[ \Sigma = \text{Var}(Y) = ZGZ^T + R \]

\[ = \sigma_S^2 \begin{bmatrix} J & & \\ & J & \\ & & \ddots \end{bmatrix} \]

\[ = \sigma_S^2 \begin{bmatrix} J \\ J \\ \vdots \end{bmatrix} \]

\[ = \sigma_e^2 I + \sigma_S^2 J \]

where \( J \) is a matrix of ones.
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

\[ Y = X\beta + e^* \]

where

\[ R = \text{Var}(e^*) \]

\[ = \begin{bmatrix} \sigma_e^2 I + \sigma_S^2 J \\
\vdots \\
\sigma_e^2 I + \sigma_S^2 J \end{bmatrix} \]
Replace the mixed model

\[ Y = X\beta + Zu + e \]

with the model

\[ Y = X\beta + e^* \]

where

\[
Var(Y) = Var(e^*) = \begin{bmatrix}
W & 0 & \cdots & 0 \\
0 & W & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
0 & 0 & \cdots & W
\end{bmatrix}
\]
First Order Autoregressive: AR(1)

\[ W = \sigma^2 \begin{bmatrix}
1 & \rho & \rho^2 & \rho^3 \\
\rho & 1 & \rho & \rho^2 \\
\rho^2 & \rho & 1 & \rho \\
\rho^3 & \rho^2 & \rho & 1
\end{bmatrix} \]

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