HUDM 5123 - Linear Models and Experimental Design
12 - Repeated Measures - Modeling Covariance Patterns

1 Repeatedly Measured Data

When data are repeatedly measured, modeling with OLS regression is typically inappropriate because the data violate the assumption of independent error terms. Last class we introduced the random intercept model, which includes a subject-specific term to account for overall subject differences. We also saw that one of the implications of using the random intercept model is that the variance/covariance matrix for the repeated measures data is assumed to follow a compound symmetric form, meaning that (a) the variance of the outcome is identical for each measurement occasion and (b) the covariances between measurement occasions are all identical. Although this assumption is less stringent than complete independence, which does not allow for any non-zero covariances between measurement occasions, it is often the case that compound symmetry is too restrictive as well. In that case, one solution is to add one or more random effects to the slopes models of the level-2 equations, which bring additional flexibility to the form of the variance/covariance matrix.

2 Data Example

The Riesby data are described in Hedeker & Gibbons (p. 52). The study focused on the longitudinal relationship between imiprimine (IMI) and desipramine (DMI) plasma levels and clinical response in 66 depressed inpatients. IMI is a tricyclic antidepressant that biotransofrms into DMI. In this study, 29 patients were classified as nonendogenous and the remaining 37 as endogenous, where nonendogenous depression is associated with some tragic life event and endogenous depression is not. Following a placebo period of 1 week, patients received 225 mg/day doses of IMI for four weeks. Subjects were rated with the Hamilton Depression Rating Scale (HDRS) at the beginning of the study and again at the end of every week. Plasma levels of IMI and DMI were also recorded every week, and the sex and age of each patient was recorded, along with their diagnosis as either nonendogenous or endogenous.

We will investigate two research questions. First, is there a relationship between time and depression? In other words, is the medication effective? Second, is there a relationship, either a main effect or interaction with time, between diagnosis (nonendogenous vs endogenous) and depression? The first six rows of the data, arranged in wide format:

```
   id endog wk0 wk1 wk2 wk3 wk4 wk5
1 101     0  26  22  18   7   4   3
2 103     0  33  24  15  24  15  13
3 104     1  29  22  18  13  19   0
4 105     0  22  12  16  16  13   9
5 106     1  21  25  23  18  20  NA
6 107     1  21  21  16  19  NA   6
```

Let's examine (a) the extent to which observations at different time points are related and, further, (b) the extent to which compound symmetry (or the necessary implication of

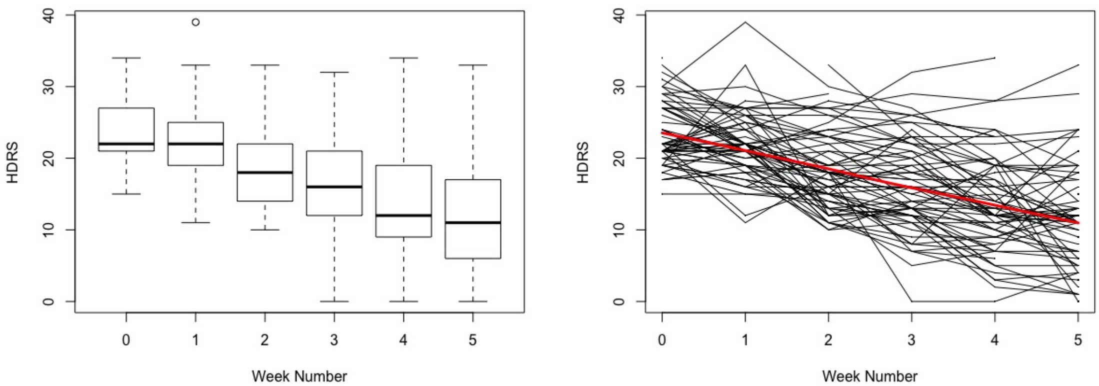

Figure 1: Boxplot and spaghetti plot of the HDRS depression ratings by week

Table 1: Means and standard deviations by time of observation

	wk0	wk1	wk2	wk3	wk4	wk5
Mean	23.40	21.80	18.30	16.40	13.60	11.90
SD	4.50	4.70	5.50	6.40	7.00	7.20

compound symmetry, sphericity) appears to hold with these data. A good first step is to estimate the variance/covariance and correlation matrixes from the data themselves.

Table 2: Covariance (on left) and correlation (on right) matrixes for the observed data

	wk0	wk1	wk2	wk3	wk4	wk5		wk0	wk1	wk2	wk3	wk4	wk5
wk0	20.55	10.11	10.14	10.09	7.19	6.28	wk0	1.00	0.49	0.41	0.33	0.23	0.18
wk1	10.11	22.07	12.28	12.55	10.26	7.72	wk1	0.49	1.00	0.49	0.41	0.31	0.22
wk2	10.14	12.28	30.09	25.13	24.63	18.38	wk2	0.41	0.49	1.00	0.74	0.67	0.46
wk3	10.09	12.55	25.13	41.15	37.34	23.99	wk3	0.33	0.41	0.74	1.00	0.82	0.57
wk4	7.19	10.26	24.63	37.34	48.59	30.51	wk4	0.23	0.31	0.67	0.82	1.00	0.65
wk5	6.28	7.72	18.38	23.99	30.51	52.12	wk5	0.18	0.22	0.46	0.57	0.65	1.00

3 Mixed Effects Regression Models (following Hedeker & Gibbons, 2006)

The violation of the independence assumption must be handled somehow in order to make correct inferences. Mixed effects models incorporate account for the correlations between repeated measures indirectly, for example, by modeling the subject id as a random effect. In such a model, each subject is assumed to have a subject-specific intercept, which, once subtracted yields independent data.

Consider the simple linear regression model for the measurement y of individual i ($i =$

$1, 2, \ldots, N$ subjects) on occasion j ($j = 1, 2, \ldots, n_i$ occasions):

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \epsilon_{ij},$$

where $\epsilon_{ij} \sim N(0, \sigma^2)$. This model assumes residual independence, which we know to be violated. To account for the dependence, we extend the model to include a term that represents the intercept for individual i on his or her repeated observations. This random intercept is denoted ν_{0i} and the model is expressed as follows.

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \nu_{0i} + \epsilon_{ij}.$$

Here, ν_{0i} represents a subject-specific effect of each individual on his or her repeated measures and the ν_{0i} are assumed $\nu_{0i} \sim N(0, \sigma^2_\nu)$. Another way to express this same model is as a *hierarchical linear model* by partitioning it into level 1 and level 2 models. The level 1 model:

$$y_{ij} = b_{0i} + b_{1i} t_{ij} + \epsilon_{ij},$$

with level 2 model:

$$\begin{aligned} b_{0i} &= \beta_0 + \nu_{0i}, \\ b_{1i} &= \beta_1. \end{aligned}$$

As we have already seen, the variance and covariance of the outcome can be expressed as follows:

$$\begin{aligned} V(y_{ij}) &= \sigma^2_\nu + \sigma^2, \\ Cov(y_{ij}, y_{ij'}) &= \sigma^2_\nu. \end{aligned}$$

Expressing the covariance as a correlation yields the intraclass correlation.

3.1 Matrix Notation

If p is the number of fixed parameters and r the number of random parameters, the mixed effects model can be succinctly expressed in matrix notation as

$$\underset{n_i \times 1}{\mathbf{y}_i} = \underset{n_i \times p}{\mathbf{X}_i} \underset{p \times 1}{\boldsymbol{\beta}} + \underset{n_i \times r}{\mathbf{Z}_i} \underset{r \times 1}{\boldsymbol{\nu}_i} + \underset{n_i \times 1}{\boldsymbol{\epsilon}_i},$$

with $i = 1, \ldots, N$ individuals and $j = 1, \ldots, n_i$ observations for individual i. $\mathbf{y}_i$ is the dependent variable vector for individual i, $\mathbf{X}_i$ is the covariate matrix for individual i, $\boldsymbol{\beta}$ is the vector of fixed regression parameters, $\mathbf{Z}_i$ is the design matrix for the random effects, $\boldsymbol{\nu}_i$ is the vector of random individual effects, and $\boldsymbol{\epsilon}_i$ is the error vector. The distributional assumptions about the errors are

$$\begin{aligned} \boldsymbol{\epsilon}_i &\sim N\left(\mathbf{0}, \sigma^2_\epsilon \mathbf{I}_{n_i}\right), \\ \boldsymbol{\nu}_i &\sim N\left(\mathbf{0}, \Sigma_\nu\right). \end{aligned}$$

The variance/covariance matrix of the repeated measures is of the form

$$V(\mathbf{y}_i) = \mathbf{Z}_i \boldsymbol{\Sigma}_\nu \mathbf{Z}_i' + \sigma^2_\epsilon \mathbf{I}_{n_i}.$$

For the example above, with four repeated measurements and a random intercept for subject, we would have

$$\mathbf{y}_i = \begin{bmatrix} y_{i1} \\ y_{i2} \\ y_{i3} \\ y_{i4} \end{bmatrix}, \quad \mathbf{X}_i = \begin{bmatrix} 1 & t_{i1} \\ 1 & t_{i1} \\ 1 & t_{i3} \\ 1 & t_{i4} \end{bmatrix}, \quad \mathbf{Z}_i = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix}, \quad \boldsymbol{\beta} = \begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}, \quad \boldsymbol{\nu}_i = \begin{bmatrix} \nu_{0i} \end{bmatrix}$$

.

Thus, the variance/covariance matrix for this random intercept mixed effects model is

$$\begin{aligned}
V(\mathbf{y}_i) &= \mathbf{Z}_i \boldsymbol{\Sigma}_\nu \mathbf{Z}_i' + \sigma^2 \mathbf{I}_{n_i} \\
&= \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \begin{bmatrix} \sigma_\nu^2 \end{bmatrix} \begin{bmatrix} 1 & 1 & 1 & 1 \end{bmatrix} + \sigma^2 \begin{bmatrix} 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \\ 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{bmatrix} \\
&= \begin{bmatrix} \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 \\ \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 \\ \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 \\ \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 \end{bmatrix} + \begin{bmatrix} \sigma_\epsilon^2 & 0 & 0 & 0 \\ 0 & \sigma_\epsilon^2 & 0 & 0 \\ 0 & 0 & \sigma_\epsilon^2 & 0 \\ 0 & 0 & 0 & \sigma_\epsilon^2 \end{bmatrix} \\
&= \begin{bmatrix} \sigma_\epsilon^2 + \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 \\ \sigma_\nu^2 & \sigma_\epsilon^2 + \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 \\ \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\epsilon^2 + \sigma_\nu^2 & \sigma_\nu^2 \\ \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\nu^2 & \sigma_\epsilon^2 + \sigma_\nu^2 \end{bmatrix}.
\end{aligned}$$

Although we did not model the variance/covariance matrix explicitly, the specification of a random intercept led to a specific form of variance/covariance matrix, the implication of which is that assumption that each persons observations have homogeneous variance across the four time points and homogenous, but potentially non-zero, covariance across repeated measurement occasions. This form of variance/covariance matrix is called *compound symmetric*.

4 Covariance Pattern Modeling

In the previous section, we used the addition of a subject-specific random effect to account for the violation of the independence assumption. We were able to see that the random intercept specification led to the covert assumption that the compound symmetry matrix is sufficient to describe the dependencies over repeated measures for each subject. It is also possible, however, to explicitly model the covariate matrix as a substitute for using random effects. This approach is called *covariance pattern modeling (CPM)*.

The general CPM may be specified as follows:

$$\underset{n_i \times 1}{\mathbf{y}_i} = \underset{n_i \times p}{\mathbf{X}_i} \underset{p \times 1}{\boldsymbol{\beta}} + \underset{n_i \times 1}{\boldsymbol{\epsilon}_i},$$

where $\boldsymbol{\epsilon}_i \sim N(\mathbf{0}, \boldsymbol{\Sigma}_i)$. The essential difference here is that we are allowing the variance/covariance matrix to be explicitly modeled. Some possible choices for the form of $\boldsymbol{\Sigma}$:

- **Independence.**

$$\boldsymbol{\Sigma} = \sigma^2 \begin{bmatrix} 1 & 0 & 0 & 0 \\ & 1 & 0 & 0 \\ & & 1 & 0 \\ & & & 1 \end{bmatrix} = \begin{bmatrix} \sigma^2 & 0 & 0 & 0 \\ & \sigma^2 & 0 & 0 \\ & & \sigma^2 & 0 \\ & & & \sigma^2 \end{bmatrix}$$

- **Compound symmetry.**

$$\boldsymbol{\Sigma} = \sigma^2 \begin{bmatrix} 1.0 & \rho & \rho & \rho \\ & 1.0 & \rho & \rho \\ & & 1.0 & \rho \\ & & & 1.0 \end{bmatrix} = \begin{bmatrix} \sigma_b^2 + \sigma_e^2 & \sigma_b^2 & \sigma_b^2 & \sigma_b^2 \\ & \sigma_b^2 + \sigma_e^2 & \sigma_b^2 & \sigma_b^2 \\ & & \sigma_b^2 + \sigma_e^2 & \sigma_b^2 \\ & & & \sigma_b^2 + \sigma_e^2 \end{bmatrix}$$

- **First-order auto-regressive.**

$$\boldsymbol{\Sigma} = \sigma^2 \begin{bmatrix} 1.0 & \rho & \rho^2 & \rho^3 \\ & 1.0 & \rho & \rho^2 \\ & & 1.0 & \rho \\ & & & 1.0 \end{bmatrix}$$

- **Unstructured.**

$$\boldsymbol{\Sigma} = \begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ & & \sigma_3^2 & \sigma_{34} \\ & & & \sigma_4^2 \end{bmatrix}$$