EPID 766: Analysis of Longitudinal Data from Epidemiologic Studies

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1.1   Review of 3 study designs

1. Cross-sectional study:

   - Information on the disease status (Y) and the exposure status (X) is obtained from a random sample at **one time point**. A snap shot of population.

   - A single observation of each variable of interest is measured from each subject: (Y_i, X_i) $(i = 1, ..., n)$. Regression such as logistic regression (if Y_i is binary) can be used to assess the **association** between Y and X:

   $$\log\left(\frac{\mathrm{P}[Y_i = 1 | X_i]}{1 - \mathrm{P}[Y_i = 1 | X_i]}\right) = \beta_0 + \beta_1 X_i$$

   $$\beta_1 = \log\left(\frac{\mathrm{P}[Y = 1 | X = 1]/(1 - \mathrm{P}[Y = 1 | X = 1])}{\mathrm{P}[Y = 1 | X = 0]/(1 - \mathrm{P}[Y = 1 | X = 0])}\right)$$

   $\beta_1 = $ log odds-ratio between exposure population $(X = 1)$ and non exposure population $(X = 0)$. $\beta_1 > 0 \implies$ the exposure population has a higher probability of getting the disease.

- Data (Y_i, X_i) can be summarized as

	$Y = 1$	$Y = 0$
$X = 1$	n_{11}	n_{10}
$X = 0$	n_{01}	n_{00}

then the MLE of β_1 is given by

$$\widehat{\beta}_1 = \log\left(\frac{n_{11} n_{00}}{n_{10} n_{01}}\right)$$

- Feature: All numbers $n_{00}, n_{01}, n_{10}, n_{11}$ are random.

- No causal inference can be made! $\widehat{\beta}_1$ may not be stable (e.g., n_{11} may be too small). Useful public health information can be obtained, such as the proportion of people in the population with the disease, the proportion of people in the population under exposure.

- Can account for confounders in the model.

2. Prospective cohort study (follow-up study):

- A cohort with known exposure status (X) is followed over time to obtain their disease status (Y).

- A single observation of (Y) may be observed (e.g., survival study) or multiple observations of (Y) may be observed (longitudinal study).

- Stronger evidence for causal inference. Causal inference can be made if X is assigned randomly (if X is a treatment indicator in the case of clinical trials).

- When single binary $(0/1)$ Y is obtained, we have

	D	$\overline{D}$	
E	n_{11}	n_{10}	n_{1+}
$\overline{E}$	n_{01}	n_{00}	n_{0+}

Here, n_{1+} and n_{0+} are fixed (sample sizes for the exposure and non-exposure groups).

3. Retrospective (case-control) study:

- A sample with **known** disease status (D) is drawn and their exposure history (E) is ascertained. Data can be summarized as

$$
\begin{array}{c|c|c}
 & D & \overline{D} \\
\hline
E & n_{11} & n_{10} \\
\hline
\overline{E} & n_{01} & n_{00} \\
\end{array}
$$

$$
 n_{+1} n_{+0}
$$

  where the margins n_{+1} and n_{+0} are fixed numbers.

- Assuming no bias in obtaining history information on E, association between E and D can be estimated.

$$
n_{11} \sim Bin(n_{+1}, P[E|D]), \quad n_{10} \sim Bin(n_{+0}, P[E|\overline{D}]).
$$

  Odds ratio: estimate from this study

$$
\widehat{\theta} = \frac{n_{11} n_{00}}{n_{10} n_{01}}
$$

estimates the following quantity

$$\theta = \frac{P[E|D]/(1 - P[E|D])}{P[E|\overline{D}]/(1 - P[E|\overline{D}])} = \frac{P[D|E]/(1 - P[D|E])}{P[D|\overline{E}]/(1 - P[D|\overline{E}])}.$$

- If disease is rare, *i.e.*, $P[D|E] \approx 0$, $P[D|\overline{E}] \approx 0$, relative risk of disease can be approximately obtained:

$$\theta \approx \frac{P[D|E]}{P[D|\overline{E}]} = \text{relative risk}.$$

More efficient than prospective cohort study in this case.

- **Problem**: recall bias! (it is difficult to ascertain exposure history E.)

1.2   Introduction to longitudinal studies

A longitudinal study is a *prospective cohort* study where repeated measures are taken over time for each individual.

A longitudinal study is usually designed to answer the following questions:

1. How does the variable of interest **change** over time?

2. How is the (change of) variable of interest associated with treatment and other covariates?

3. How does the variable of interest relate to each other over time?

4. · · ·

1.3 Data examples

Example 1: Framingham study

In the Framingham study, each of 2634 participants was examined every 2 years for a 10 year period for his/her cholesterol level.

Study objectives:

1. How does cholesterol level **change** over time on average as people get older?

2. How is the change of cholesterol level associated with sex and baseline age?

3. Do males have more stable (true) baseline cholesterol level and change rate than females?

A subset of 200 subjects' data is used for illustrative purpose.

A glimpse of the raw data

```
newid id cholst sex age time
1 1244 175 1 32 0
1 1244 198 1 32 2
1 1244 205 1 32 4
1 1244 228 1 32 6
1 1244 214 1 32 8
1 1244 214 1 32 10
2 835 299 0 34 0
2 835 328 0 34 4
2 835 374 0 34 6
2 835 362 0 34 8
2 835 370 0 34 10
3 176 250 0 41 0
3 176 277 0 41 2
3 176 265 0 41 4
3 176 254 0 41 6
3 176 263 0 41 8
3 176 268 0 41 10
4 901 243 0 44 0
4 901 211 0 44 2
4 901 204 0 44 4
4 901 196 0 44 6
4 901 246 0 44 8
```

Cholesterol level over time for a subset of 200 subjects from Framingham study

Cholesterol levels over time
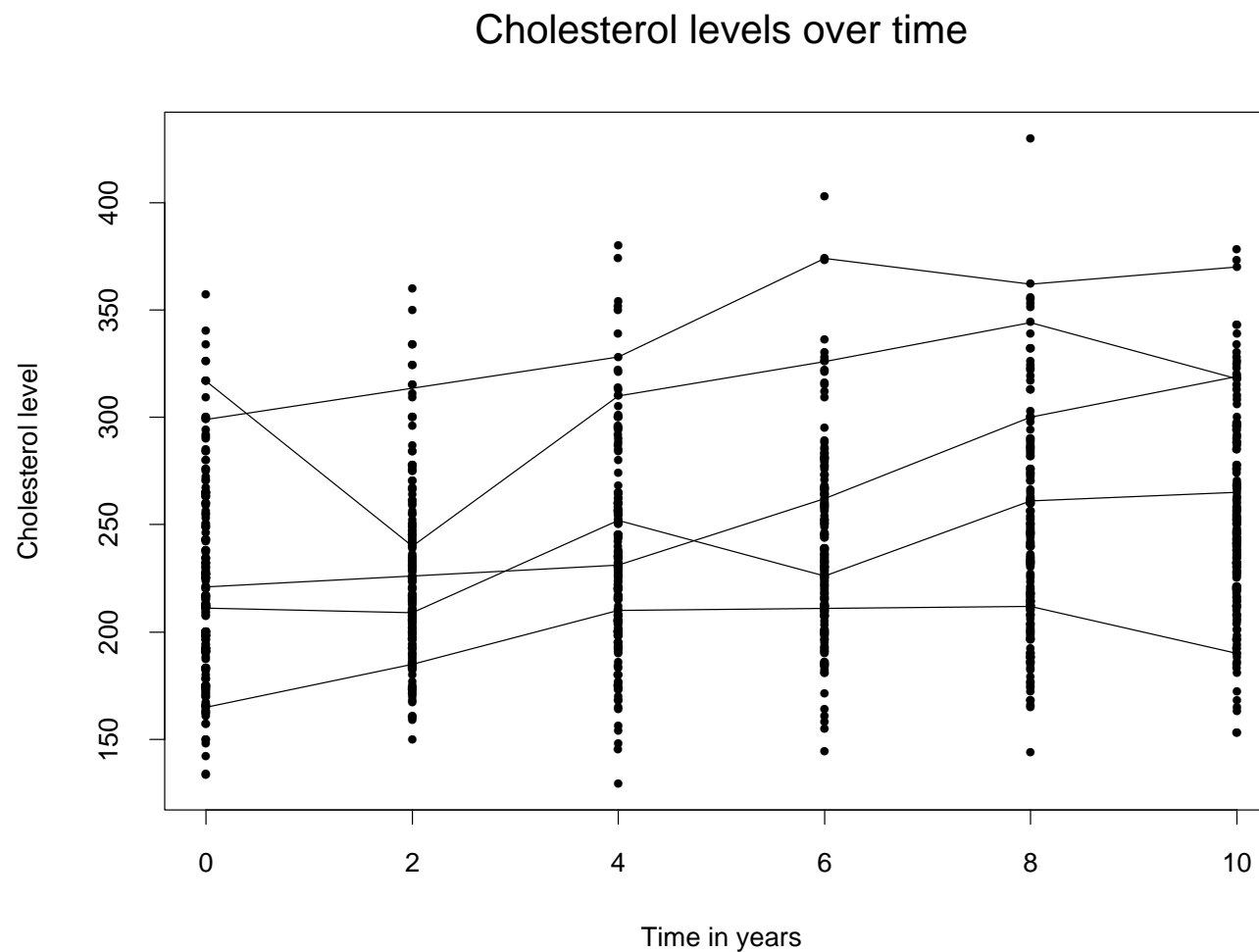
What we observed from this data set:

1. Cholesterol levels increase (linearly) over time for most individuals.

2. Each subject has his/her own trajectory line with a possibly different intercept and slope, implying two sources of variations: within and between subject variations.

3. Each subject has on average 5 observations (as opposed to one observation per subject for a cross-sectional study)

4. The data is not balanced. Some individuals have missing observations (e.g., subject 2's Cholesterol is missing at $time = 2$)

5. The inference is NOT limited to these 200 individuals. Instead, the inference is for the target population and each subject is viewed as a **random** person drawn from the target population.

Example 2: Respiratory Infection Disease

Each of 275 Indonesian preschool children was examined up to six consecutive quarters for the presence of respiratory infection (yes/no). Information on age, sex, height for age, xerophthalmia (vitamin A deficiency) was also obtained.

Study objectives:

- Was the risk of respiratory infection related to vitamin A deficiency after adjusting for age, sex, and height for age, etc.?

Features of this data set:

1. Outcome is whether or not a child has respiratory infection, i.e., binary outcome.

2. Some covariates (age, vitamin A deficiency and height) are time-varying covariates and some are one-time covariates.

A glimpse of the infection data

Print the first 20 observations   1

Obs	id	infect	xero	sex	visit	season
1	121013	0	0	0	1	2
2	121013	0	0	0	2	3
3	121013	0	0	0	3	4
4	121013	0	0	0	4	1
5	121013	1	0	0	5	2
6	121013	0	0	0	6	3
7	121113	0	0	1	1	2
8	121113	0	0	1	2	3
9	121113	0	0	1	3	4
10	121113	0	0	1	4	1
11	121113	1	0	1	5	2
12	121113	0	0	1	6	3
13	121114	0	0	0	1	2
14	121114	0	0	0	2	3
15	121114	0	0	0	3	4
16	121114	1	0	0	4	1
17	121114	1	0	0	5	2
18	121114	0	0	0	6	3
19	121140	0	0	1	1	2
20	121140	0	1	1	2	3

Proportions of respiratory infection and vitamin A deficiency
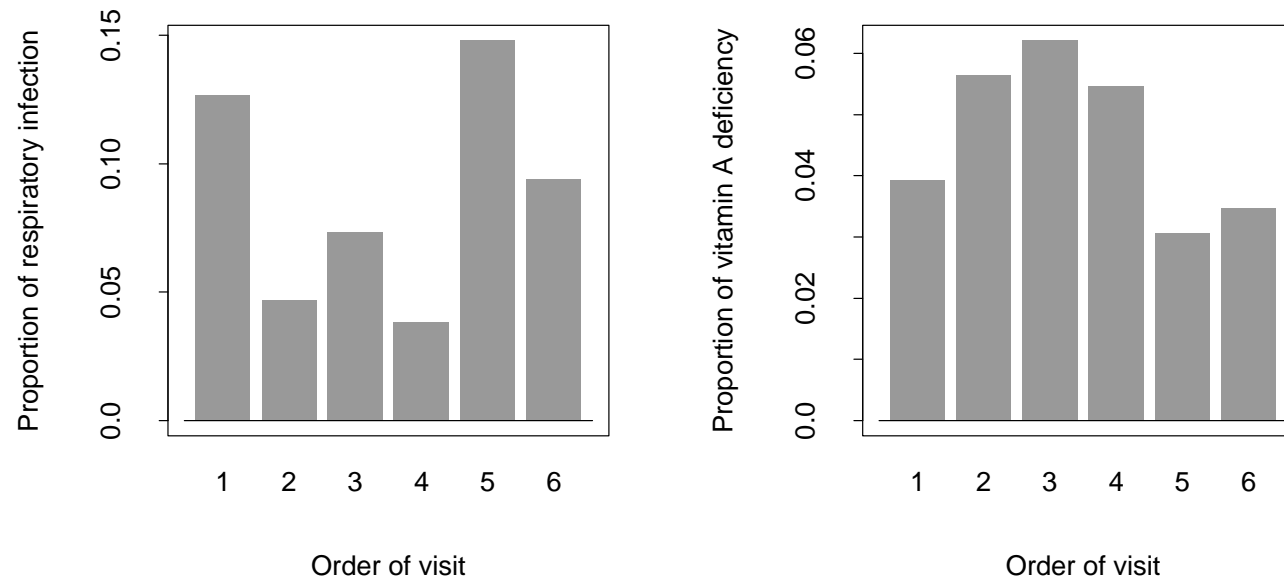
Example 3: Epileptic seizure counts from the progabide trial

In the progabide trial, 59 epileptics were randomly assigned to receive the anti-epileptic treatment (progabide) or placebo. The number of seizure counts was recorded in 4 consecutive 2-week intervals. Age and baseline seizure counts (in an eight week period prior to the treatment assignment) were also recorded.

Study objectives:

- Does the treatment work?

- What is the treatment effect adjusting for available covariates?

Features of this data set:

1. Outcome is count data, implying a Poisson regression.

2. Baseline seizure counts were for 8 weeks, as opposed to 2 weeks for other seizure counts.

3. Randomization may be taken into account in the data analysis.

A glimpse of the seisure data

Print the first 20 observations   1

Obs	id	seize	trt	interval	age
1	101	76	1	8	18
2	101	11	1	2	18
3	101	14	1	2	18
4	101	9	1	2	18
5	101	8	1	2	18
6	102	38	1	8	32
7	102	8	1	2	32
8	102	7	1	2	32
9	102	9	1	2	32
10	102	4	1	2	32
11	103	19	1	8	20
12	103	0	1	2	20
13	103	4	1	2	20
14	103	3	1	2	20
15	103	0	1	2	20
16	104	11	0	8	31
17	104	5	0	2	31
18	104	3	0	2	31
19	104	3	0	2	31
20	104	3	0	2	31

Epileptic seizure counts from the progabide trial

Seizure counts for progabide arm

Seizure counts for control arm
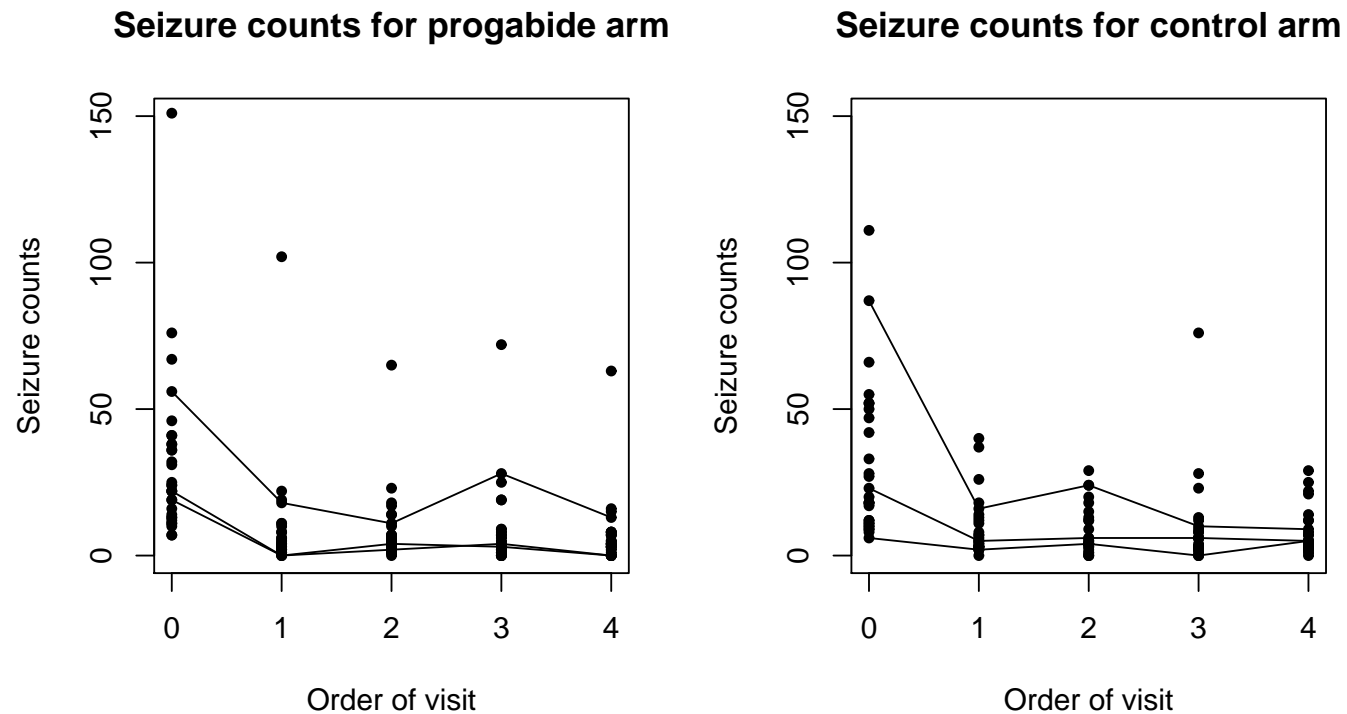
1.4   Features of longitudinal data

Common features of all examples:

- Each subject has multiple time-ordered observations of response.

- Responses from the same subjects may be "more alike" than others.

- Inference is NOT in study subjects, but in population from which they are from.

- # of subjects $>>$ # of observations/subject

- *Source of variations* – *between* and *within* subject variations.

Difference in the examples:

- Different types of responses (continuous, binary, count).

- Objectives depend on the type of study – "mean" behavior, etc.

Comparison of data structures:

Classical study		Longitudinal study		
Subject	Data	Subject	Data	Time
1	x_1	1	$x_{11}, x_{12}, ..., x_{15}$	$t_{11}, t_{12}, ..., t_{15}$
	y_1		$y_{11}, y_{12}, ..., y_{15}$	$t_{11}, t_{12}, ..., t_{15}$
2	x_2	2	$x_{21}, x_{22}, ..., x_{25}$	$t_{21}, t_{22}, ..., t_{25}$
	y_2		$y_{21}, y_{22}, ..., y_{25}$	$t_{21}, t_{22}, ..., t_{25}$

For simplicity, we consider one covariate case.

1.5　Why longitudinal studies?

1. A longitudinal study allows us to study the *change* of the variable of interest over time, either at population level or individual level.

2. A longitudinal study enables us to separately estimate the cross-sectional effect (e.g., cohort effect) and the longitudinal effect (e.g., aging effect):

   Given $y_{ij}, \mathrm{age}_{ij}$ $(j = 1, 2, \cdots, n_i, j = 1$ is the baseline). In a cross-sectional study, $n_i = 1$ and we are forced to fit the following model

   $$y_{i1} = \beta_0 + \beta_C \mathrm{age}_{i1} + \varepsilon_{i1}.$$

   That is, β_C is the cross-sectional effect of age.

   With longitudinal data $(n_i > 1)$, we can entertain the model

   $$y_{ij} = \beta_0 + \beta_C \mathrm{age}_{i1} + \beta_L (\mathrm{age}_{ij} - \mathrm{age}_{i1}) + \varepsilon_{ij}.$$

Then

$$y_{i1} = \beta_0 + \beta_C \text{age}_{i1} + \varepsilon_{i1} \quad (\text{let } j = 1),$$

$$y_{ij} - y_{i1} = \beta_L(\text{age}_{ij} - \text{age}_{i1}) + \varepsilon_{ij} - \varepsilon_{i1}.$$

That is, β_L is the longitudinal effect of age and in general $\beta_L \neq \beta_C$.

3. A longitudinal study is more powerful to detect an association of interest compared to a cross-sectional study, $\Longrightarrow$ more efficient, less sample size (number of subjects).

4. A longitudinal study allows us to study the *within-subject* and *between-subject* variations.

   Suppose $b \sim (\mu, \sigma_b^2)$ is the blood pressure for a patient population. However, what we observe is $Y = b + \varepsilon$, where $\varepsilon \sim (0, \sigma_\varepsilon^2)$ is the measurement error.

   - $\sigma_\varepsilon^2 = $ within-subject variation

   - $\sigma_b^2 = $ between-subject variation

If we have only one observation Y_i for each subject from a sample of n patients, then we can't separate σ_ε^2 and σ_b^2. Although we can use data $Y_1, Y_2, ..., Y_n$ to make inference on μ, we can't make any inference on σ_b^2.

However, if we have repeated (or longitudinal) measurements Y_{ij} of blood pressure for each subjects, then

$$Y_{ij} = b_i + \varepsilon_{ij}.$$

Now, it is possible to make inference about all quantities μ, σ_b^2 and σ_ε^2.

5. A longitudinal study provides more evidence for possible causal interpretation.

1.6   Challenges in analyzing longitudinal data

Key assumptions in a classical regression model: There is only one observation of response per subject, $\Longrightarrow$ responses are *independent* to each other. For example, when $y =$ cholesterol level,

$$y_i = \beta_0 + \beta_1 \text{sex}_i + \beta_2 \text{age}_i + \varepsilon_i.$$

However, the observations from the same subject in a longitudinal study tend to be more similar to each other than those observations from other subjects, $\Longrightarrow$ responses (from the same subjects) are not independent any more. **Although**, the observations from *different* subjects are still independent.

What happens if we treat observations as independent (i.e., ignore the correlation)?

1. In general, the estimation of the associations (regression coefficients) of the outcome and covariates is valid.

2. However, the variability measures (e.g, the SEs from a classical regression analysis) are not right: sometimes smaller, sometimes bigger than the true variability.

3. Therefore, the inference is not valid (too significant than it should be if the SE is too small).

Sources of variation and correlation in longitudinal data:

1. Between-subject variation: For the blood pressure example, if each subject's blood pressures were measured within a relatively short time, then the following model may be a reasonable one:

$$y_{ij} = b_i + \varepsilon_{ij},$$

where b_i is the true blood pressure of subject i with variance σ_b^2, ε_{ij} is the independent (random) measurement error with variance σ_ε^2, independent of b_i.

For $j \neq k$,

$$
\begin{aligned}
\operatorname{corr}(y_{ij}, y_{ik}) &= \frac{\operatorname{cov}(y_{ij}, y_{ik})}{\sqrt{\operatorname{var}(y_{ij})\operatorname{var}(y_{ik})}} \\
&= \frac{\sigma_b^2}{\sigma_b^2 + \sigma_\varepsilon^2}.
\end{aligned}
$$

Therefore, if the between-subject variation $\sigma_b^2 \neq 0$, then data from the same subjects are correlated.

The blood pressure example
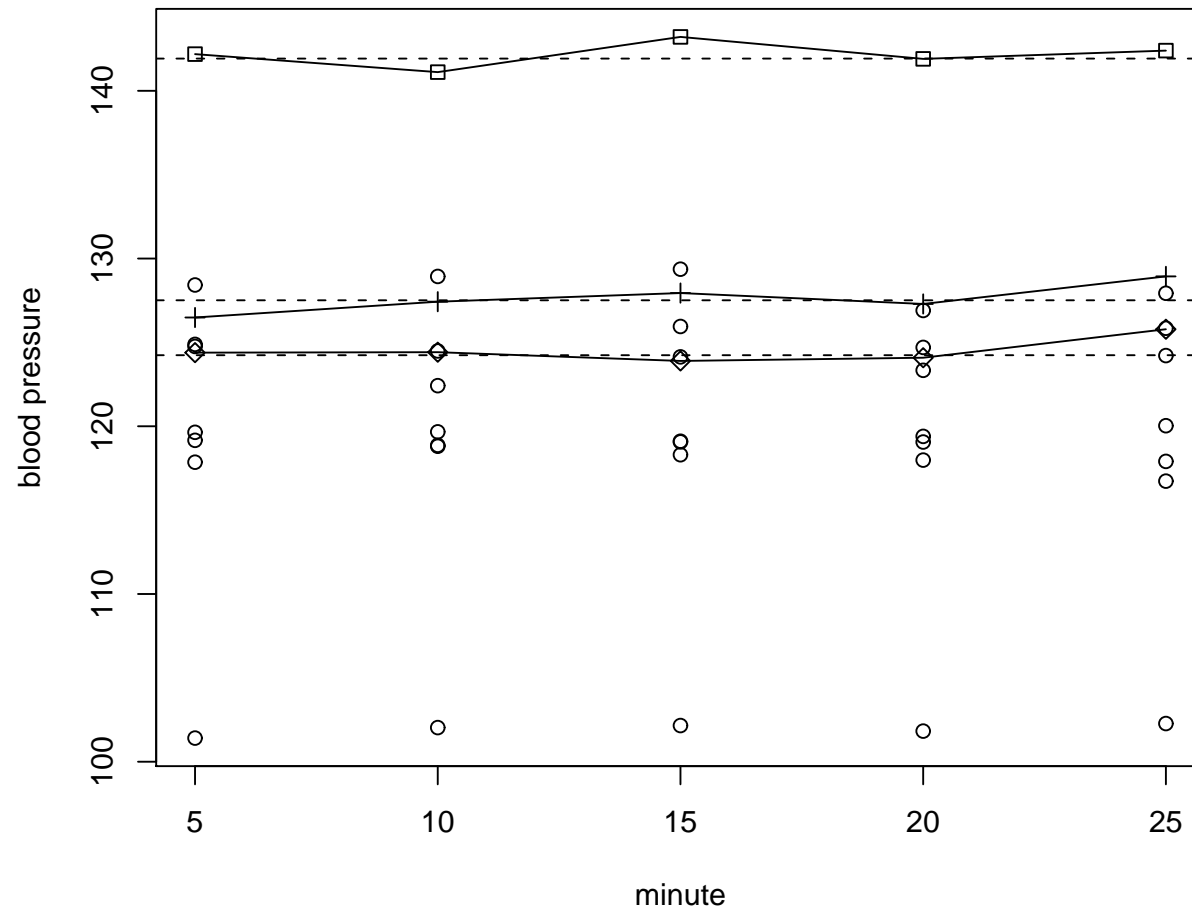
2. Serial correlation: If the time intervals between blood pressure measurements are relatively large so it may not be reasonable to assume a constant blood pressure for each subject:

$$y_{ij} = b_i + U_i(t_{ij}) + \varepsilon_{ij},$$

where $b_i =$ true long-term blood pressure, $U_i(t_{ij}) =$ a stochastic process (like a time series) due to biological fluctuation of blood pressure, ε_{ij} is the independent (random) measurement error. Here the correlation is caused by both b_i and $U_i(t_{ij})$.

3. In a typical longitudinal study for human where $\#$ of observations/subject is small to moderate, there may not be enough information for the serial correlation and most correlation can be accounted for by (possibly complicated) between-subject variation.

1.7   Methods for analyzing longitudinal data

1. Two-stage: summarize each subject's outcome and regress the summary statistics on *one-time* covariates. Especially useful for continuous longitudinal data. However, this method is getting out-dated since the mixed model approach can do the same thing even better.

2. Mixed (effects) model approach: model fixed effects and random effects; use random effects to model correlation.

3. Generalized estimating equation (GEE) approach: model the dependence of marginal mean on covariates. Correlation is not a main interest. Particularly good for discrete data.

4. Transition models: use history as covariates. Good for prediction of future response using history.

1.8 Two-stage method for analyzing longitudinal data

- Outcome (usually continuous): $y_{i1}, ..., y_{in_i}$ measured at $t_{i1}, ..., t_{in_i}$; one-time covariates: $x_{i1}, ..., x_{ip}$.

- Two-stage analysis is conducted as follows:

  1. Stage 1: Get summary statistics from subject i's data: $y_{i1}, ..., y_{in_i}$. For example, use mean $\bar{y}_i = (y_{i1} + \cdots + y_{in_i})/n_i$ or fit a linear regression for each subject:

     $$y_{ij} = b_{i0} + b_{i1}t_{ij} + \varepsilon_{ij},$$

     and get estimates $\widehat{b}_{i0}$, $\widehat{b}_{i1}$ of b_{i0} and b_{i1}. Here we assume that subject i's **true** response at time t_{ij} is given by

     $$b_{i0} + b_{i1}t_{ij},$$

     a straight line. Suppose $t = 0$ is the baseline, then b_{i0} is subject i's **true** response at baseline and b_{i1} is subject i's change rate of

the **true** response (not y). The error term ε_{ij} can be regarded as measurement error.

2. Stage 2: Treat the summary statistics as new responses and regress the summary statistics on one-time covariates. For example, after we got $\widehat{b}_{i0}$ and $\widehat{b}_{i1}$, we can calculate the means of $\widehat{b}_{i0}$ and $\widehat{b}_{i1}$ and the standard errors of those means, compare $\widehat{b}_{i0}$, $\widehat{b}_{i0}$ among genders, or do the following regressions

$$\widehat{b}_{i0} = \alpha_0 + \alpha_1 x_{i1} + \cdots + \alpha_p x_{ip} + e_{i0}$$
$$\widehat{b}_{i1} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip} + e_{i1}.$$

Here, α_k is the effect of x_k on the **true** baseline response (not y), β_k is the effect of x_k on the change rate of of the **true** response.

1.9   Analyzing Framingham data using two-stage method

Example 1(a) The Framingham study:

- Stage I: For each subject, fit

$$y_{ij} = b_{i0} + b_{i1}t_{ij} + \varepsilon_{ij}.$$

  and get estimates $\widehat{b}_{i0}$ and $\widehat{b}_{i1}$.

SAS program for stage I:

```
options ls=80 ps=200;

data cholst;
   infile "cholst.dat";
   input newid id cholst sex age time;
run;

proc sort;
   by newid time;
run;

proc print data=cholst (obs=20);
   var newid cholst sex age time;
run;
```

```
title "First stage in two-stage analysis";
proc reg outest=out noprint;
  model cholst = time;
  by newid;
run;

data out; set out;
  b0hat = intercept;
  b1hat = time;
  keep newid b0hat b1hat;
run;

data main; merge cholst out;
  by newid;
  if first.newid=1;
run;

title "Summary statistics for intercepts and slopes";
proc means mean stderr var t probt;
  var b0hat b1hat;
run;

title "Correlation between intercepts and slopes";
proc corr;
 var b0hat b1hat;
run;
```

Part of output from above SAS program:

```
                 Summary statististics for intercepts and slopes                 2

                             The MEANS Procedure

     Variable            Mean        Std Error          Variance     t Value     Pr > |t|
     -----------------------------------------------------------------------------------
     b0hat        220.6893518        2.9478698          1737.99       74.86       <.0001
     b1hat          2.5502529        0.2566421       13.1730374        9.94       <.0001
     -----------------------------------------------------------------------------------


                 Correlation between intercepts and slopes                        3

                             The CORR Procedure

                    2  Variables:     b0hat     b1hat

                             Simple Statistics

     Variable       N        Mean      Std Dev            Sum      Minimum       Maximum

     b0hat        200   220.68935     41.68917          44138    141.14286     360.16667
     b1hat        200     2.55025      3.62947      510.05058    -14.00000      11.74286


                   Pearson Correlation Coefficients, N = 200
                          Prob > |r| under H0: Rho=0

                                   b0hat             b1hat

             b0hat               1.00000          -0.26939
                                                   0.0001

             b1hat              -0.26939           1.00000
                                 0.0001
```

Summary statistics from stage 1:

Parameter	mean	SE	t	$P[T \geq |t|]$	
$\widehat{b}_0$	221	3	75	$< .0001$	
$\widehat{b}_1$	2.55	0.257	10	$< .0001$	$\widehat{\mathrm{corr}}(\widehat{b}_0, \widehat{b}_1) = -0.27$

$$S^2_{\widehat{b}_0} = 1738, \qquad S^2_{\widehat{b}_1} = 13.2.$$

Note:

1. Similar to the blood pressure example, we can use the sample means of $\widehat{b}_0$ and $\widehat{b}_1$ to estimate the means of b_0 and b_1. Hence we can use sample mean of $\widehat{b}_1$ (2.55) its SE (0.257) to answer the first objective of this study.

2. However, since $\mathrm{var}(\widehat{b}_{i0})$ and $\mathrm{var}(\widehat{b}_{i1})$ contain variability due to estimating the **true** baseline response b_{i0} and change rate b_{i1} for individual i, so

$$\mathrm{var}(\widehat{b}_{i0}) > \mathrm{var}(b_{i0}), \quad \mathrm{var}(\widehat{b}_{i1}) > \mathrm{var}(b_{i1}).$$

Sample variances $S^2_{\widehat{b}_0}$ and $S^2_{\widehat{b}_1}$ are unbiased estimates of $\text{var}(\widehat{b}_{i0})$ and $\text{var}(\widehat{b}_{i1})$ and would overestimate $\text{var}(b_{i0})$ and $\text{var}(b_{i1})$.

3. Similarly,

$$\text{corr}(\widehat{b}_0, \widehat{b}_1) \neq \text{corr}(b_0, b_1).$$

Therefore, $\widehat{\text{corr}}(\widehat{b}_0, \widehat{b}_1) = -0.27$ cannot be used to estimate the correlation between the *true* baseline response b_0 and *true* change rate b_1.

4. We will use mixed model approach to address the above issues later.

- Stage II:

  1. Try to compare $\mathrm{E}(b_0)$ and $\mathrm{E}(b_1)$ between males and females.

  2. Try to compare $\mathrm{var}(b_0)$ and $\mathrm{var}(b_1)$ between males and females.

  3. Try to examine the effects of age and sex on b_0 using

  $$\widehat{b}_0 = \alpha_0 + \alpha_1 \mathrm{sex} + \alpha_2 \mathrm{age} + e_0.$$

  Technically, we should use b_0 instead of $\widehat{b}_0$. However, $\widehat{b}_0$ is an unbiased estimate of b_0 (and b_0 is not observable), so using $\widehat{b}_0$ is valid.

  4. Try to examine the effects of age and sex on b_1 using

  $$\widehat{b}_1 = \beta_0 + \beta_1 \mathrm{sex} + \beta_2 \mathrm{age} + e_1.$$

  Similar to the above argument, using $\widehat{b}_1$ here is valid.

SAS program for stage II:

```
title "Test equality of mean and variance of intercepts and slopes between sexes";
proc ttest;
   class sex;
   var b0hat b1hat;
run;

title "Regression to look at the association between intercept and sex, age";
proc reg data=main;
   model b0hat = sex age;
run;

title "Regression to look at the association between slope and sex, age";
proc reg data=main;
   model b1hat = sex age;
run;
```

Part of output from above SAS program:

```
     Test equality of mean and variance of intercepts and slopes between sexes      4

                                The TTEST Procedure

                                 Variable:  b0hat

      sex             N        Mean      Std Dev       Std Err       Minimum      Maximum

      0              97       224.0      40.2259        4.0843        146.3        348.1
      1             103       217.6      42.9885        4.2358        141.1        360.2
      Diff (1-2)             6.3629      41.6719        5.8960

    sex        Method          Mean       95% CL Mean       Std Dev      95% CL Std Dev

    0                         224.0      215.9     232.1     40.2259     35.2522   46.8465
    1                         217.6      209.2     226.0     42.9885     37.8123   49.8197
    Diff (1-2)  Pooled        6.3629    -5.2640   17.9898    41.6719     37.9405   46.2237
    Diff (1-2)  Satterthwaite 6.3629    -5.2408   17.9666

               Method          Variances          DF      t Value      Pr > |t|

               Pooled          Equal                198       1.08        0.2818
               Satterthwaite   Unequal           197.99       1.08        0.2809

                              Equality of Variances

               Method        Num DF     Den DF     F Value     Pr > F

               Folded F        102         96        1.14       0.5117
```

Variable: b1hat

sex	N	Mean	Std Dev	Std Err	Minimum	Maximum
0	97	1.7454	3.3567	0.3408	-14.0000	8.3000
1	103	3.3083	3.7282	0.3673	-11.3750	11.7429
Diff (1-2)		-1.5629	3.5529	0.5027		

sex	Method	Mean	95% CL Mean		Std Dev	95% CL Std Dev	
0		1.7454	1.0688	2.4219	3.3567	2.9417	3.9092
1		3.3083	2.5796	4.0369	3.7282	3.2793	4.3206
Diff (1-2)	Pooled	-1.5629	-2.5542	-0.5716	3.5529	3.2348	3.9410
Diff (1-2)	Satterthwaite	-1.5629	-2.5511	-0.5747			

Method	Variances	DF	t Value	Pr > |t|
Pooled	Equal	198	-3.11	0.0022
Satterthwaite	Unequal	197.61	-3.12	0.0021

Equality of Variances

Method	Num DF	Den DF	F Value	Pr > F
Folded F	102	96	1.23	0.2996

Regression to look at the association between intercept and sex, age   5

The REG Procedure
Model: MODEL1
Dependent Variable: b0hat

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	53715	26857	18.11	<.0001
Error	197	292145	1482.96718		
Corrected Total	199	345859			

Root MSE	38.50931	R-Square	0.1553	
Dependent Mean	220.68935	Adj R-Sq	0.1467	
Coeff Var	17.44956			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	138.21793	15.04083	9.19	<.0001
sex	1	-9.75053	5.47862	-1.78	0.0767
age	1	2.05576	0.34820	5.90	<.0001

Regression to look at the association between slope and sex, age   6

The REG Procedure
Model: MODEL1
Dependent Variable: b1hat

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	257.85057	128.92528	10.75	<.0001
Error	197	2363.58387	11.99789		
Corrected Total	199	2621.43443			

Root MSE	3.46380	R-Square	0.0984	
Dependent Mean	2.55025	Adj R-Sq	0.0892	
Coeff Var	135.82170			

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	1	6.14089	1.35288	4.54	<.0001
sex	1	1.73654	0.49279	3.52	0.0005
age	1	-0.10538	0.03132	-3.36	0.0009

- Summary from Stage II:

  1. Comparison of $\mathrm{E}(b_0)$ and $\mathrm{E}(b_1)$ between males and females:

     $$\widehat{\mathrm{E}}(\widehat{b}_0) : 223.97(\text{female}), 217.6(\text{male}), \text{p-value} = 0.28$$

     $$\widehat{\mathrm{E}}(\widehat{b}_1) : 1.75(\text{female}), 3.31(\text{male}), \text{p-value} = 0.002.$$

  2. Comparison of $\mathrm{var}(b_0)$ and $\mathrm{var}(b_1)$ between males and females:

     $$S^2_{\widehat{b}_0} : 1621(\text{female}), 1848(\text{male}), \text{p-value} = 0.5$$

     $$S^2_{\widehat{b}_1} : 11.3(\text{female}), 13.9(\text{male}), \text{p-value} = 0.3.$$

     However, the above tests do NOT compare $\mathrm{var}(b_0)$ and $\mathrm{var}(b_1)$ between males and females. We will use mixed model approach to address this problem.

  3. Model for **true** baseline response b_0:

     $$\widehat{b}_0 \;=\; \alpha_0 + \alpha_1\mathrm{sex} + \alpha_2\mathrm{age} + e_0,$$

     $$\widehat{\alpha}_0 = 138.2(15.0), \quad \widehat{\alpha}_1 = -9.75(5.5), \quad \widehat{\alpha}_2 = 2.06(0.35).$$

After adjusting for sex, one year increase in age corresponds to 2 unit increase in baseline cholesterol level. After adjusting for baseline age, on average males' baseline cholesterol level is about 10 units less than females'.

4. Model for change rate of the **true** response b_1:

$$\widehat{b}_1 = \beta_0 + \beta_1 \text{sex} + \beta_2 \text{age} + e_1,$$
$$\widehat{\beta}_0 = 6.14(1.35), \quad \widehat{\beta}_1 = 1.74(0.5), \quad \widehat{\beta}_2 = -0.11(0.03).$$

After adjusting for sex, one year increase in age corresponds to 0.11 less in cholesterol level change rate. After adjusting for baseline age, males' cholesterol level change rate is 1.74 greater than females'.

Some remarks on two-stage analysis:

1. The first stage model should be reasonably good for the second stage analysis to be valid and make sense.

2. Two-stage analysis can only be used when the covariates considered are one-time covariates (fixed over time).

3. Summary statistics of a time-varying covariates cannot be used in the second stage analysis because of error in variable issue.

4. When the covariates considered are time-varying covariates, two-stage analysis is not appropriate. Mixed effects modeling or GEE approach can be used.

5. Two-stage analysis can be applied to discrete response (binary or count data). However, mixed effect modeling or GEE approach can be more flexible.

6. Although two-stage approach can be used to make inference on the quantities of interest, it is less efficient compared to the mixed

model approach. Therefore, mixed model approach should be used whenever possible.

2   Linear mixed models for normal longitudinal data

- What is a linear mixed model?

  1. Random intercept model

  2. Random intercept and slope model

  3. Other error structures

  4. General mixed models

- Estimation and inference

- Choose a variance matrix of the data

- Analyze Framingham data using linear mixed models

- GEE for mixed models, missing data issue

2.1   What is a linear mixed (effects) model?

A linear mixed model is an extension of a linear regression model to model longitudinal (correlated) data. It contains *fixed effects* and *random effects* where random effects are subject-specific and are used to model between-subject variation and the correlation induced by this variation.

What are fixed effects? Fixed effects are the covariate effects that are fixed across subjects in the study sample. These effects are the ones of our particular interest. E.g., the regression coefficients in usual regression models are fixed effects:

$$y = \alpha + x\beta + \varepsilon.$$

What are random effects? Random effects are the covariate effects that vary among subjects. So these effects are subject-specific and hence are random (unobservable) since each subject is a random subject drawn from a population.

I. Random intercept only model:

Data from m subjects:

Subject	Outcome	Time	Random intercept
1	$y_{11}, y_{12}, ..., y_{1n_1}$	$t_{11}, t_{12}, ..., t_{1n_1}$	b_1
2	$y_{21}, y_{22}, ..., y_{2n_2}$	$t_{21}, t_{22}, ..., t_{2n_2}$	b_2
...			
i	$y_{i1}, y_{i2}, ..., y_{in_i}$	$t_{i1}, t_{i2}, ..., t_{in_i}$	b_i
...			
m	$y_{m1}, y_{m2}, ..., y_{mn_m}$	$t_{m1}, t_{m2}, ..., t_{mn_m}$	b_m

Other covariates: $x_{ij2}, ..., x_{ijp}, i = 1, ..., m, j = 1, ..., n_i$.

A random intercept model assumes:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_i + \varepsilon_{ij}.$$

Random intercept model:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_i + \varepsilon_{ij}$$

where β's are *fixed* effects of interest, $b_i \sim N(0, \sigma_b^2)$ are random effects, $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$ are independent (measurement)errors.

Interpretation of the model components:

1. From model,

$$\mathrm{E}[y_{ij}] = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp}.$$

2. β_k: Average increase in y associated with one unit increase in x_k, the kth covariate.

3. $\beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_i = true$ response for subject i at t_{ij}.

4. $\beta_0 + b_i$ is the intercept for subject $i \implies b_i =$ deviation of intercept of subject i from population intercept β_0.

5. σ_b^2 = between-subject variance, σ_ε^2 = within-subject variance.

6. Total variance of y: $\mathsf{Var}(y_{ij}) = \sigma_b^2 + \sigma_\varepsilon^2$, constant over time.

7. Correlation between y_{ij} and $y_{ij'}$:

$$corr(y_{ij}, y_{ij'}) = \frac{\sigma_b^2}{\sigma_b^2 + \sigma_\varepsilon^2} = \rho$$

8. Correlation is constant and positive.

Why treat b_i as random

1. Treating b_i as random enables us to make inference for the whole population from which the sample was drawn. Treating b_i as fixed would only allow us to make inference for the study sample.

2. Usually n_i is small for longitudinal studies. Therefore, as the number of total data points gets larger, the number of b_i (which is m, the number of subjects) gets large proportionally. In this case, the standard properties (such as consistency) of the parameter estimates may not still hold if b_i is treated as fixed.

When no x, random intercept only model reduces to

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + b_i + \varepsilon_{ij}.$$

Graphical representation of data from random intercept model
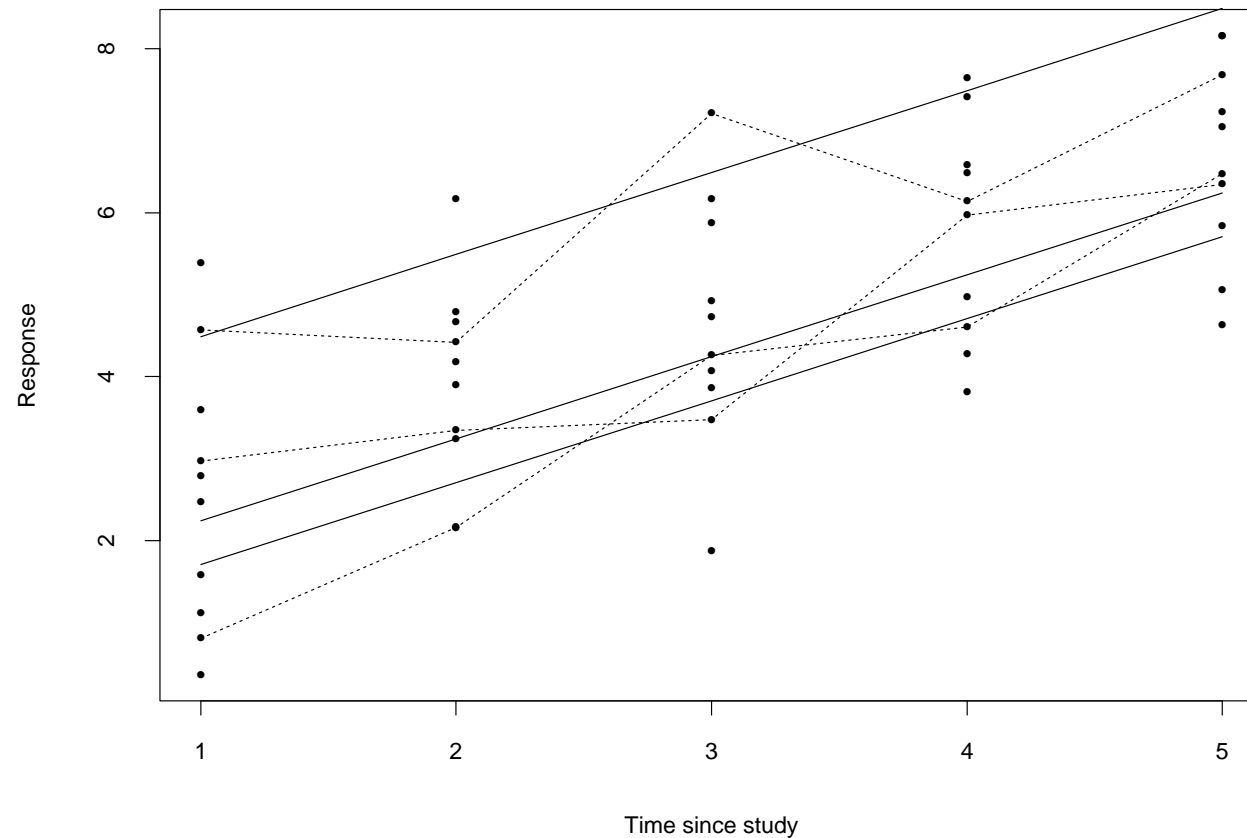
II. Random intercept and slope model:

Data from m subjects:

Subject	Outcome	Time	Random intercept	Random slope
1	$y_{11}, ..., y_{1n_1}$	$t_{11}, ..., t_{1n_1}$	b_{10}	b_{11}
2	$y_{21}, ..., y_{2n_2}$	$t_{21}, ..., t_{2n_2}$	b_{20}	b_{21}
...				
i	$y_{i1}, ..., y_{in_i}$	$t_{i1}, ..., t_{in_i}$	b_{i0}	b_{i1}
...				
m	$y_{m1}, ..., y_{mn_m}$	$t_{m1}, ..., t_{mn_m}$	b_{m0}	b_{m1}

Other covariates: $x_{ij2}, ..., x_{ijp}, i = 1, ..., m, j = 1, ..., n_i.$

A random intercept and slope model assumes:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}.$$

Random intercept and slope model:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij},$$

β_k the same as before, random effects b_{i0}, b_{i1} are assumed to have a bivariate normal distribution

$$\begin{pmatrix} b_{i0} \\ b_{i1} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{bmatrix} \right).$$

Usually, no constraint is imposed on σ_{ij}; $\varepsilon_{ij} \sim N(0, \sigma_\varepsilon^2)$.

Interpretation of the model components:

1. Mean structure is the same as before:

$$\mathrm{E}[y_{ij}] = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp}.$$

2. β_k: Average increase in y associated with one unit increase in x_k, the kth covariate.

3. $\beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_{i0} + b_{i1} t_{ij} = true$ response for

subject i at t_{ij}.

4. $\beta_0 + b_i$ = the intercept for subject $i \implies b_{i0}$ = deviation of intercept of subject i from population intercept β_0

5. $\beta_1 + b_{i1}$ = the slope for subject $i \implies b_{i1}$ = deviation of slope of subject i from population slope β_1

6. $Var(b_{i0} + b_{i1}t_{ij}) = \sigma_{00} + 2t_{ij}\sigma_{01} + t_{ij}^2\sigma_{11}$ = between-subject variance (varying over time).

7. σ_ε^2 = within-subject variance.

8. Total variance of y: $\text{Var}(y_{ij}) = \sigma_{00} + 2t_{ij}\sigma_{01} + t_{ij}^2\sigma_{11} + \sigma_\varepsilon^2$, not a constant over time.

9. Correlation between y_{ij} and $y_{ij'}$: not a constant over time.

When no x, random intercept and slope model reduces to

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}.$$

Graphical representation of data from random intercept and slope model
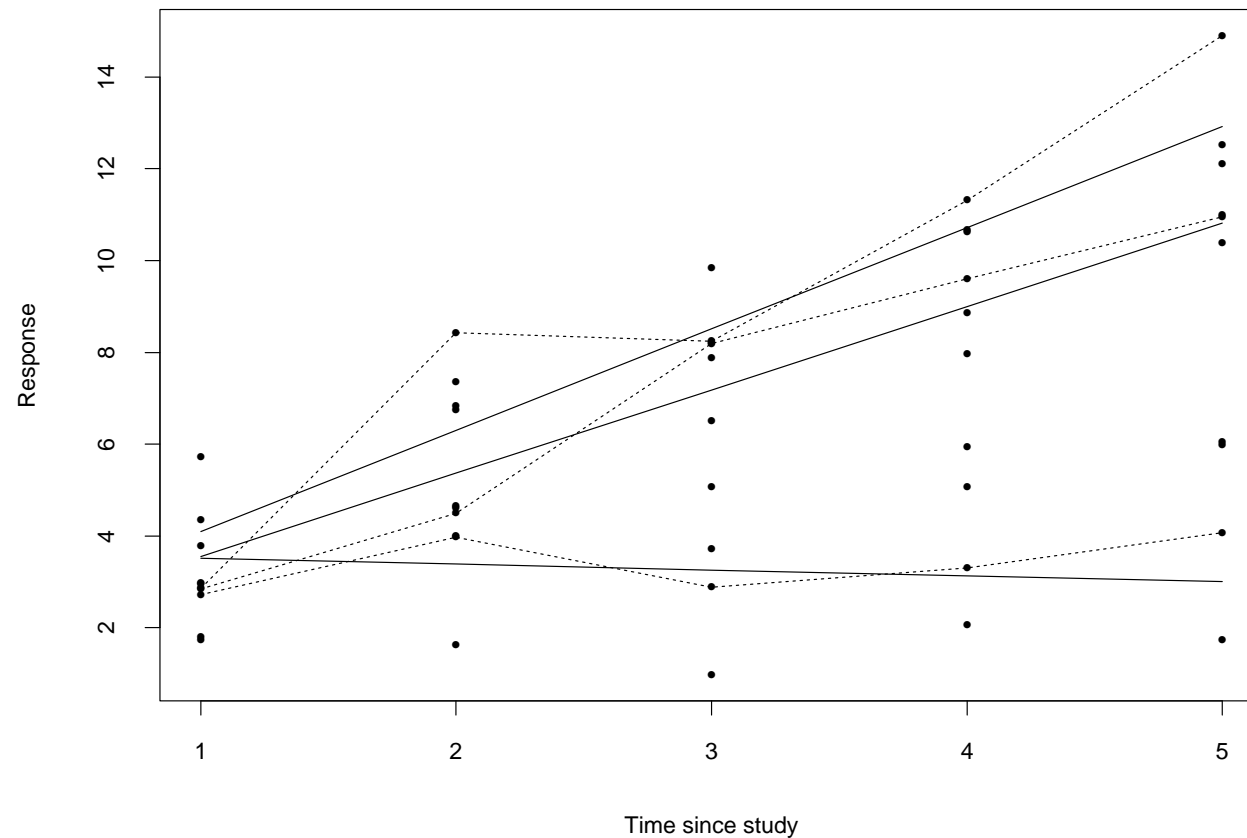
III. Other mixed models:

- A correlated error model

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + e_{ij},$$

  where e_{ij} are correlated normal errors (may contain random effects and ε_{ij}).

  For example,

  1. Compound symmetric (exchangeable) variance matrix

  $$\begin{pmatrix} e_{i1} \\ e_{i2} \\ e_{i3} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \sigma^2 \begin{bmatrix} 1 & \rho & \rho \\ \rho & 1 & \rho \\ \rho & \rho & 1 \end{bmatrix} \right).$$

  Here, $-1 < \rho < 1$. A random intercept model is almost equivalent to this model.

2. AR(1) variance matrix

$$
\begin{pmatrix} e_{i1} \\ e_{i2} \\ e_{i3} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \sigma^2 \begin{bmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{bmatrix} \right).
$$

Here, $-1 < \rho < 1$. It assumes that the error $(e_{i1}, e_{i2}, e_{i3})^T$ is an autoregressive process with order 1. This structure is more appropriate if y is measured at equally spaced time points.

3. Spatial power variance matrix

$$
\begin{pmatrix} e_{i1} \\ e_{i2} \\ e_{i3} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \sigma^2 \begin{bmatrix} 1 & \rho^{|t_2 - t_1|} & \rho^{|t_3 - t_1|} \\ \rho^{|t_2 - t_1|} & 1 & \rho^{|t_3 - t_2|} \\ \rho^{|t_3 - t_1|} & \rho^{|t_3 - t_2|} & 1 \end{bmatrix} \right).
$$

Here, $0 < \rho < 1$. This error structure reduces to AR(1) when y is measured at equally spaced time points. This structure is appropriate if y is measured at unequally spaced time points.

4. Unstructured variance matrix

$$
\begin{pmatrix} e_{i1} \\ e_{i2} \\ e_{i3} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma_{22} & \sigma_{23} \\ \sigma_{13} & \sigma_{23} & \sigma_{33} \end{bmatrix} \right).
$$

Here no restriction is imposed on σ_{ij}. This structure may be used only if (potential) time points are the same for all subjects and the number is relatively small.

IV. General linear mixed models

General model 1: fixed effects + random effects + pure measurement error:

For example,

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij},$$

where ε_{ij} is the pure measurement error (has an independent variance structure).

Software to implement the above model: `Proc Mixed` in SAS:

```
Proc Mixed data= method=;
  class id;
  model y = t x / s;   /* specify t x for fixed effects */
  random intercept t / subject=id type=un; /* specify the covariance matrix */
                                   /* for random effects */
  repeated / subject=id type=vc; /* specify the variance structure for error */
run;
```

vc = variance component (idependent error)

General model 2: fixed effects + random effects + stochastic process

For example,

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + b_{i0} + b_{i1} t_{ij} + U_i(t_{ij}),$$

where $U_i(t)$ is a stochastic process with AR(1), a spatial power variance structure, or other variance structure.

Software to implement the above model: `Proc Mixed` in SAS:

```
Proc Mixed data= method=;
  class id;
  model y = t x / s;   /* specify t x for fixed effects */
  random intercept t / subject=id type=un; /* specify the covariance matrix */
                                      /* for random effects */
  repeated / subject=id type=sp(pow)(t); /* specify the variance structure for error */
run;
```

If the time points are equally spaced, we can use `type=ar(1)` in the repeated statement for AR(1) variance structure for $U_i(t)$:

```
    repeated cat_t / subject=id type=ar(1); /* cat_t is class t   */
```

General model 3: fixed effects + random effects + stochastic process + pure measurement error

For example,

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + b_{i0} + b_{i1} t_{ij} + U_i(t_{ij}) + \varepsilon_{ij},$$

where $U_i(t)$ is a stochastic process with some variance structure (*e.g.*,a spatial power variance structure), ε_{ij} is the pure measurement error.

Software to implement the above model: `Proc Mixed` in SAS:

```
Proc Mixed data= method=;
  class id;
  model y = t x / s;  /* specify t x for fixed effects */
  random intercept t / subject=id type=un; /* specify the covariance matrix */
                                    /* for random effects */
  repeated / subject=id type=sp(pow)(t) local; /* specify error variance structure */
run;
```

If the time points are equally spaced, we can use `type=ar(1)` in the repeated statement if assuming AR(1) for $U_i(t)$:

```
repeated cat_t / subject=id type=ar(1) local; /* cat_t is class t  */
```

General model 4: fixed effects + un-structured error

For example,

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + e_{ij},$$

where e_{ij} is the error with un-structured variance matrix

Software to implement the above model: `Proc Mixed` in SAS:

```
Proc Mixed data= method=;
  class id;
  model y = t x / s;   /* specify t x for fixed effects */
  repeated cat_t / subject=id type=un;   /* specify error variance structure */
run;
```

Note that no "random" statement can be used in the above model. When the number of different time points is big, there will be too many parameters to estimate.

2.2   Estimation and inference for linear mixed models

Let θ consist of all parms in random effects (e.g., b_{i0}, b_{i1}) and errors (ε_{ij}). We want to make inference on β and θ. There are two approaches:

1. Maximum likelihood:

$$\ell(\beta, \theta; y) = logL(\beta, \theta; y).$$

   Maximize $\ell(\beta, \theta; y)$ jointly w.r.t. β and θ to get their MLEs.

2. Restricted maximum likelihood (REML):

   (a) Get REML of θ from a REML likelihood $\ell_{REML}(\theta; y)$ (take into account the estimation of β). Leads to less biased $\widehat{\theta}$. For example, in a linear regression model

$$\widehat{\sigma}^2_{REML} = \frac{\text{Residual Sum of Squares}}{n - p - 1}.$$

   (b) Estimate β by maximizing $\ell(\beta, \widehat{\theta}_{REML}; y)$.

Hypothesis Testing

- After we fit a linear mixed model such as

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij},$$

  SAS will output a test for each β_k, including the estimate, SE, p-value (for testing $H_0 : \beta_k = 0$), etc.

- If we want to test a contrast between β_k, we can use `estimate` statement in `Proc Mixed`. Then SAS will output the estimate, SE for the contrast and the p-value for testing the contrast is zero. See Programs 2 and 3 for Framingham data.

2.3 How to choose random effects and the error structure?

1. Use graphical representation to identify possible random effects.

2. Use biological knowledge to identify possible error structure.

3. Use information criteria to choose a final model:

   (a) Akaike's Information Criterion (AIC):

   $$AIC = -2\{\ell(\widehat{\beta}, \widehat{\theta}; y) - q\}$$

   where $q = \#$ of elements in θ. Smaller AIC is preferred.

   (b) Bayesian Information Criterion (BIC):

   $$BIC = -2\{\ell(\widehat{\beta}, \widehat{\theta}; y) - 0.5 \times q \times \log(m)\}, \quad m = \# \text{ of subjects}$$

   Again, smaller BIC is preferred.

2.4 Analyze Framingham data using linear mixed models

- Model to address **objective 1**: How does cholesterol level **change** over time on average as people get older?

  ⋆ Consider the following **basic** model suggested by the data:

  $$y_{ij} = b_{i0}^* + b_{i1}^* t_{ij} + \varepsilon_{ij} \tag{2.1}$$

  where y_{ij} is the jth cholesterol level measurement from subject i, t_{ij} is year from the beginning of the study (or baseline) and b_{i0}^*, b_{i1}^* are random variables distributed as

  $$\begin{pmatrix} b_{i0}^* \\ b_{i1}^* \end{pmatrix} \sim N \left(\begin{bmatrix} \beta_0 \\ \beta_1 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{bmatrix} \right),$$

  and ε_{ij} are independent errors distributed as $N(0, \sigma_\varepsilon^2)$.

⋆ Model (2.1) assumes that

1. The **true** cholesterol level for each individual changes linearly over time with a different intercept and slope, which are both random (since the individual is a random subject drawn from the population).

2. Since $t = 0$ is the baseline, so b_{i0}^* can be viewed as the true but unobserved cholesterol level for subject i at the baseline, and b_{i1}^* can be viewed as the change rate of the **true** cholesterol level for subject i.

3. β_0 is the population average of the **true** baseline cholesterol level of all individuals in the population, β_1 is the population average change rate of **true** cholesterol level and it tells us how cholesterol level changes on average as people get older. So β_1 is the **longitudinal effect** or **aging effect** on cholesterol level.

4. σ_{00} is the variance of the **true** baseline cholesterol level b_{i0}^*; σ_{11} is the variance of the change rate b_{i1}^* of the true

cholesterol level; and σ_{01} is the covariance between **true** baseline cholesterol level b_{i0}^* and the change rate b_{i1}^* of true cholesterol level.

⋆ The random variables b_{i0}^* and b_{i1}^* can be re-written as

$$b_{i0}^* = \beta_0 + b_{i0}, \qquad b_{i1}^* = \beta_1 + b_{i1},$$

where b_{i0}, b_{i1} have the following distribution:

$$\begin{pmatrix} b_{i0} \\ b_{i1} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{bmatrix} \right).$$

⋆ Model (2.1) then can be re-expressed as

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}. \tag{2.2}$$

Therefore, β_0, β_1 are fixed effects and b_{i0}, b_{i1} are random effects.

⋆ The following is the SAS program for fitting model (2.1):

```
title "Framingham data: mixed model without covariates";
proc mixed data=cholst;
  class newid;
  model cholst = time / s;
  random intercept time / type=un subject=newid g;
  repeated / type=vc subject=newid;
run;
```

The following is the output from the above program:

```
        Framingham data: mixed model without covariates              1

                      The Mixed Procedure

                      Model Information

        Data Set                      WORK.CHOLST
        Dependent Variable            cholst
        Covariance Structures         Unstructured, Variance
                                      Components
        Subject Effects               newid, newid
        Estimation Method             REML
        Residual Variance Method      Parameter
        Fixed Effects SE Method       Model-Based
        Degrees of Freedom Method     Containment
```

Class Level Information

Class	Levels	Values
newid	200	1 2 3 4 5 6 7 8 9 10 11 12 13 14 ...

Dimensions

Covariance Parameters	4
Columns in X	2
Columns in Z Per Subject	2
Subjects	200
Max Obs Per Subject	6
Observations Used	1044
Observations Not Used	0
Total Observations	1044

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	10899.75433605	
1	2	9960.12567386	0.00000120
2	1	9960.12082968	0.00000000

Convergence criteria met.

The Mixed Procedure

Estimated G Matrix

Row	Effect	newid	Col1	Col2
1	Intercept	1	1467.30	-2.2259
2	time	1	-2.2259	3.8409

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	newid	1467.30
UN(2,1)	newid	-2.2259
UN(2,2)	newid	3.8409
Residual	newid	434.11

Fit Statistics

-2 Res Log Likelihood	9960.1
AIC (smaller is better)	9968.1
AICC (smaller is better)	9968.2
BIC (smaller is better)	9981.3

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	939.63	<.0001

```
                    Solution for Fixed Effects

                          Standard
       Effect          Estimate        Error        DF     t Value     Pr > |t|

       Intercept       220.57          2.9305        199      75.26      <.0001
       time              2.8170        0.2408        191      11.70      <.0001


                  Type 3 Tests of Fixed Effects

                          Num       Den
            Effect         DF        DF      F Value      Pr > F

            time            1        191     136.83       <.0001
```

From this output, we see that:

1. $\widehat{\sigma}_{00} = 1467$, as compared to $\widehat{\text{var}}(\widehat{b}_0) = 1738$ from the two-stage approach.

2. $\widehat{\sigma}_{11} = 3.84$, as compared to $\widehat{\text{var}}(\widehat{b}_1) = 13.2$ from the two-stage approach.

3. $\widehat{\text{corr}}(b_{i0}^*, b_{i1}^*) = \widehat{\text{corr}}(b_{i0}, b_{i1}) = -2.2259/\sqrt{1467 \times 3.84} = -0.03$, as compared to $\widehat{\text{corr}}(\widehat{b}_0, \widehat{b}_1) = -0.27$ from the two-stage approach.

4. The estimated mean of true baseline cholesterol level is

$\widehat{\beta}_0 = 220.57$ with SE=2.93, as compared to the sample mean 220.69 of $\widehat{b}_0$ with SE $= 2.94$ from the two-stage approach.

5. The estimated change rate (longitudinal effect) $\widehat{\beta}_1 = 2.82$ with SE=0.24, as compared to the sample mean 2.55 of $\widehat{b}_1$ with SE $= 0.26$ from the two-stage approach.

6. $\widehat{\sigma}_\varepsilon^2 = 434.11$.

⋆ **Q:** Is it reasonable to assume ε_{ij} in model (2.1) to be pure measurement error?

⋆ We can consider a more general model such as AR(1) for ε_{ij} and test this assumption.

```
data cholst; set cholst;
   cat_time = time;
run;

title "Framingham data: mixed model without covariates + AR(1) error";
proc mixed data=cholst covtest;
   class newid cat_time;
   model cholst = time / s;
   random intercept time / type=un subject=newid g;
```

```
   repeated cat_time / type=ar(1) subject=newid;
run;
```

and the **relevant output**:

```
                        Covariance Parameter Estimates

                                              Standard          Z
          Cov Parm      Subject    Estimate      Error      Value         Pr Z

          UN(1,1)       newid       1478.76     174.15       8.49       <.0001
          UN(2,1)       newid      -3.5618     10.7033      -0.33       0.7393
          UN(2,2)       newid       4.1717      1.3186       3.16       0.0008
          AR(1)         newid      -0.03193     0.06156     -0.52       0.6039
          Residual                  425.06     28.4010      14.97       <.0001


                            Fit Statistics

              -2 Res Log Likelihood             9959.9
              AIC (smaller is better)           9969.9
              AICC (smaller is better)          9969.9
              BIC (smaller is better)           9986.3
```

★ **Note**:

1. P-value for testing $H_0 : \rho = 0$ is 0.6039, no strong evidence against H_0.

2. All model selection criteria lead to iid error ε_{ij}.

3. We usually don't use the above output to test variances because of the boundary issue.

- Model to investigate the cross sectional age effect and longitudinal age effect on cholesterol level:

  ⋆ Re-write the true baseline cholesterol level b_{i0} and the change rate b_{i1} in model (2.1) in terms of conditional distributions given age:

$$b_{i0}^* = \beta_0 + \beta_C age_i + b_{i0} \qquad (2.3)$$
$$b_{i1}^* = \beta_1 + \beta_A age_i + b_{i1}, \qquad (2.4)$$

  where age_i is individual i's baseline age. Note that these b_{i0} and b_{i1} are different from those in the previous model.

  Then β_C is the cross sectional age effect and $\beta_1 + \beta_A age_i$ is the longitudinal effect for the population with baseline age eqaul to age_i.

  ⋆ The *average* longitudinal effect is

$$\beta_1 + \beta_A \mathrm{E}(age),$$

which can be estimated by

$$\widehat{\beta}_1 + \widehat{\beta}_A \overline{age},$$

where $\overline{age}$ is the sample average of age.

⋆ Suggest that we can center age and use the centered age (denoted by $cent\_age_i = age_i - \overline{age}$) in (2.3). Then β_1 is the average longitudinal effect

⋆ We are interested in testing $H_0 : \beta_C = \beta_1$.

⋆ Assume the usual distribution for (b_{i0}, b_{i1}):

$$\begin{pmatrix} b_{i0} \\ b_{i1} \end{pmatrix} \sim N \left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{bmatrix} \right).$$

Here both σ_{00} and σ_{11} are the remaining variances in b_{i0}^* and b_{i1}^* after baseline age effect has been taken into account. So they should be smaller than those corresponding values in model (2.1).

$\star$ Basic model (2.1) becomes

$$
\begin{aligned}
y_{ij} &= \beta_0 + \beta_C cent\_age_i + \beta_1 t_{ij} + \beta_A cent\_age_i \times t_{ij} \\
&\quad + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij},
\end{aligned}
\tag{2.5}
$$

where $\varepsilon_{ij} \sim N(0, \sigma^2)$ are independent errors.

$\star$ The following is the SAS program for fitting model (2.5):

```
data cholst; set cholst;
  cent_age = age - 42.56;
run;

title "Framingham data: longitudinal effect vs. cohort effect";
proc mixed data=cholst;
  class newid;
  model cholst = time cent_age cent_age*time / s;
  random intercept time / type=un subject=newid g;
  repeated / type=vc subject=newid;
  estimate "long-cross" time 1 cent_age -1;
run;
```

⋆ The relevant output of the above SAS program is

```
                            Iteration History

      Iteration     Evaluations      -2 Res Log Like          Criterion

          0                   1       10826.01576300
          1                   2        9929.74817925          0.00000516
          2                   1        9929.72729664          0.00000000


                        Convergence criteria met.


                            Estimated G Matrix

      Row     Effect         newid            Col1            Col2

       1      Intercept        1           1226.69          9.7829
       2      time             1              9.7829        3.2598


                    Covariance Parameter Estimates

           Cov Parm        Subject        Estimate

           UN(1,1)          newid          1226.69
           UN(2,1)          newid             9.7829
           UN(2,2)          newid             3.2598
           Residual         newid           434.15


                            Fit Statistics

           -2 Res Log Likelihood                 9929.7
           AIC (smaller is better)               9937.7
```

```
                    AICC (smaller is better)          9937.8
                    BIC (smaller is better)           9950.9
```

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	896.29	<.0001

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	220.57	2.7172	198	81.18	<.0001
time	2.8157	0.2343	190	12.02	<.0001
cent_age	1.9861	0.3455	652	5.75	<.0001
time*cent_age	-0.1024	0.02930	652	-3.50	0.0005

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
time	1	190	144.42	<.0001
cent_age	1	652	33.05	<.0001
time*cent_age	1	652	12.22	0.0005

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
long-cross	0.8296	0.4174	652	1.99	0.0473

⋆ What we learn from this output:

1. $\widehat{\sigma}_{00} = 1226.7$, much smaller than the corresponding estimate 1467 from model (2.1) since baseline age was used to explain the variability in the true baseline cholesterol level.

2. $\widehat{\sigma}_{11} = 3.26$, much smaller than the corresponding estimate 3.84 from model (2.1) since baseline age was used to explain the variability in the true baseline cholesterol change rate.

3. $\widehat{\beta}_0 = 220.57$ is the estimate of mean true baseline cholesterol level for the individuals whose baseline age $= 42.56$ (the average age), which is the same as the one from model (2.1) but with a smaller SE (2.71 vs. 2.93).

4. The estimate of the longitudinal age effect is $\widehat{\beta}_1 = 2.8157$ with SE $= 0.2343$, which is basically the same as $\widehat{\beta}_1 = 2.8170$ with SE $= 0.24$ from model (2.1).

5. The estimate of the cross sectional age effect is $\widehat{\beta}_C = 1.99$ with SE $= 0.3455$, which is very different from the estimate of the longitudinal age effect $\widehat{\beta}_1 = 2.82$.

6. The P-value for testing $H_0 : \beta_L = \beta_C$ is 0.0473, significant at level 0.05!

7. $\widehat{\sigma}_\varepsilon^2 = 434.15$ is basically the same as the corresponding estimate from model (2.1), which is 434.11.

8. Similarly, we can test $iid\ \varepsilon_{ij}$ by considering correlated errors such as AR(1) for ε_{ij} and test to see if $\rho = 0$.

- Model to address **objective 2**: How is the change of cholesterol level associated with sex and baseline age?

  ⋆ Re-write the true baseline cholesterol level b_{i0} and the change rate b_{i1} in model (2.1) in terms of conditional distribution given gender and baseline age:

  $$b_{i0}^* = \beta_0 + sex_i\beta_{0,sex} + age_i\beta_{0,age} + b_{i0} \qquad (2.6)$$
  $$b_{i1}^* = \beta_1 + sex_i\beta_{1,sex} + age_i\beta_{1,age} + b_{i1}, \qquad (2.7)$$

  where we assume that b_{i0}, b_{i1} have the following distribution

  $$\begin{pmatrix} b_{i0} \\ b_{i1} \end{pmatrix} \sim N\left(\begin{bmatrix} 0 \\ 0 \end{bmatrix}, \begin{bmatrix} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{bmatrix}\right).$$

  ⋆ Then $\beta_{0,sex}, \beta_{0,age}$ are the sex effect and baseline age effect on the baseline cholesterol level. Of course, β_0 does **NOT** have a proper interpretation.

⋆ Similarly, $\beta_{1,sex}, \beta_{1,age}$ are the sex effect and baseline age effect on the change rate of the true cholesterol level, and β_1 does **NOT** have a proper interpretation.

⋆ Substituting the above expressions into model (2.1), we got

$$y_{ij} = \beta_0 + sex_i\beta_{0,sex} + age_i\beta_{0,age} + \beta_1 t_{ij}$$
$$+ sex_i t_{ij}\beta_{1,sex} + age_i t_{ij}\beta_{1,age} + b_{i0} + b_{i1}t_{ij} + \varepsilon_{ij}. \quad (2.8)$$

⋆ Suppose we also want to **test** whether or not the change rates between 30 years old males and 40 years old females are the same using the above model.

⋆ From model (2.7), the (average) change rate of 30 years old males is

$$\beta_1 + 1 \times \beta_{1,sex} + 30 \times \beta_{1,age} = \beta_1 + \beta_{1,sex} + 30\beta_{1,age}.$$

The (average) change rate of 40 years old females is

$$\beta_1 + 0 \times \beta_{1,sex} + 40 \times \beta_{1,age} = \beta_1 + 40\beta_{1,age}.$$

The difference between these two rates is

$$\beta_1 + \beta_{1,sex} + 30\beta_{1,age} - (\beta_1 + 40\beta_{1,age}) = \beta_{1,sex} - 10\beta_{1,age}.$$

Therefore, we need only to test $H_0 : \beta_{1,sex} - 10\beta_{1,age} = 0$.

$\star$ We can use the following SAS program to answer our questions.

```
title "Framingham data: how baseline cholesterol level and";
title2" change rate depend on sex and baseline age";
proc mixed data=cholst;
  class newid;
  model cholst = sex age time sex*time age*time / s;
  random intercept time / type=un subject=newid g s;
  repeated / type=vc subject=newid;
  estimate "rate-diff" sex*time 1 age*time -10;
run;
```

⋆ Part of the relevant output from above program is

```
                Framingham data: how baseline cholesterol level and              1
                     change rate depend on sex and baseline age

                               Iteration History

        Iteration     Evaluations      -2 Res Log Like          Criterion

            0                   1        10813.99587154
            1                   2         9907.89014721          0.00000655
            2                   1         9907.86364103          0.00000000


                          Convergence criteria met.


                             Estimated G Matrix

           Row     Effect        newid         Col1           Col2

            1     Intercept        1          1209.89         13.5502
            2     time             1          13.5502          2.5211


                       Covariance Parameter Estimates

                    Cov Parm       Subject      Estimate

                    UN(1,1)         newid        1209.89
                    UN(2,1)         newid        13.5502
                    UN(2,2)         newid         2.5211
                    Residual        newid        434.15
```

Fit Statistics

```
-2 Res Log Likelihood              9907.9
AIC (smaller is better)            9915.9
AICC (smaller is better)           9915.9
BIC (smaller is better)            9929.1
```

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	906.13	<.0001

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	138.18	14.9148	197	9.26	<.0001
sex	-9.6393	5.4352	652	-1.77	0.0766
age	2.0509	0.3454	652	5.94	<.0001
time	6.8003	1.2229	189	5.56	<.0001
sex*time	1.7995	0.4536	652	3.97	<.0001
age*time	-0.1145	0.02835	652	-4.04	<.0001

Solution for Random Effects

Effect	newid	Estimate	Std Err Pred	DF	t Value	Pr > |t|
Intercept	2	100.50	11.5761	651	8.68	<.0001
time	2	2.7414	1.2643	651	2.17	0.0305
Intercept	74	46.9844	11.0096	651	4.27	<.0001
time	74	1.3579	1.2525	651	1.08	0.2787
Intercept	171	-51.5764	11.3046	651	-4.56	<.0001
time	171	-0.6812	1.2583	651	-0.54	0.5885

Estimates

Label	Estimate	Standard Error	DF	t Value	Pr > |t|
rate-diff	2.9441	0.5606	651	5.25	<.0001

⋆ What we learn from this output:

1. $\widehat{\beta}_{0,sex} = -9.64$ (SE $= 5.43$), so after adjusting for baseline age, males' baseline cholesterol level is about 10 units less than females'.

2. $\widehat{\beta}_{0,age} = 2.05$ (SE $= 0.35$), so after adjusting for gender, one year older people's baseline cholesterol level is about 2 units higher than that of one year younger people.

3. $\widehat{\beta}_{1,sex} = 1.80$ (SE $= 0.45$), so after adjusting for baseline age, males' change rate is 1.80 (cholesterol unit/year) greater that females' change rate. Similar estimate from 2-stage analysis is 1.74 (SE=0.49).

4. $\widehat{\beta}_{1,age} = -0.11$ (SE $= 0.028$), so after adjusting for sex, one year older people's change rate is 0.11 less than one year younger people's change rate. Similar estimate from 2-stage analysis is -0.11 (SE=0.031).

5. The change rate difference of interest is 2.94 (SE $= 0.56$). Significantly different!

6. $\widehat{\sigma}_{00} = 1210$, which is smaller than the corresponding estimate from model (2.5) since we use both age and gender to explain the variability in baseline true cholesterol level.

7. $\widehat{\sigma}_{11} = 2.52$, which is smaller than the corresponding estimate from model (2.5) since we use both age and gender to explain the variability in the cholesterol level change rate.

8. $\widehat{\sigma}_{\varepsilon}^2 = 434.15$, basically the same as its estimates from models (2.1) and (2.5).

9. Similarly, we can test $iid\ \varepsilon_{ij}$ by considering correlated errors such as AR(1).

⋆ **Note**: The models (2.6) and (2.7) for b_{i0} and b_{i1} are basically the same as the second stage models in the two stage analysis for the Framingham data.

⋆ Compare results from this model to the results from the two-stage analysis:

(a) Effect on baseline cholesterol level:

Model (2.8) : $\widehat{\beta}_0 = 138.18(SE = 14.9),$

$\widehat{\beta}_{0,sex} = -9.64(SE = 5.43),\ \widehat{\beta}_{0,age} = 2.05(SE = 0.35)$

Two-stage : $\widehat{\alpha}_0 = 138.2(SE = 15.0),$

$\widehat{\alpha}_1 = -9.75(SE = 5.48),\ \widehat{\alpha}_2 = 2.06(SE = 0.35).$

(b) Effect on change rate of cholesterol level:

Model (2.8) : $\widehat{\beta}_1 = 6.80(SE = 1.22),$

$\widehat{\beta}_{1,sex} = 1.80(SE = 0.45), \widehat{\beta}_{1,age} = -0.11(SE = 0.03)$

Two-stage : $\widehat{\beta}_0 = 6.14(SE = 1.35),$

$\widehat{\beta}_1 = 1.74(SE = 0.49),\ \widehat{\beta}_2 = -0.11(SE = 0.03).$

⋆ We can also estimate the individual random effects and estimate their trajectory lines.

⋆ Estimated subject-specific lines from model (2.8):

Cholesterol levels over time
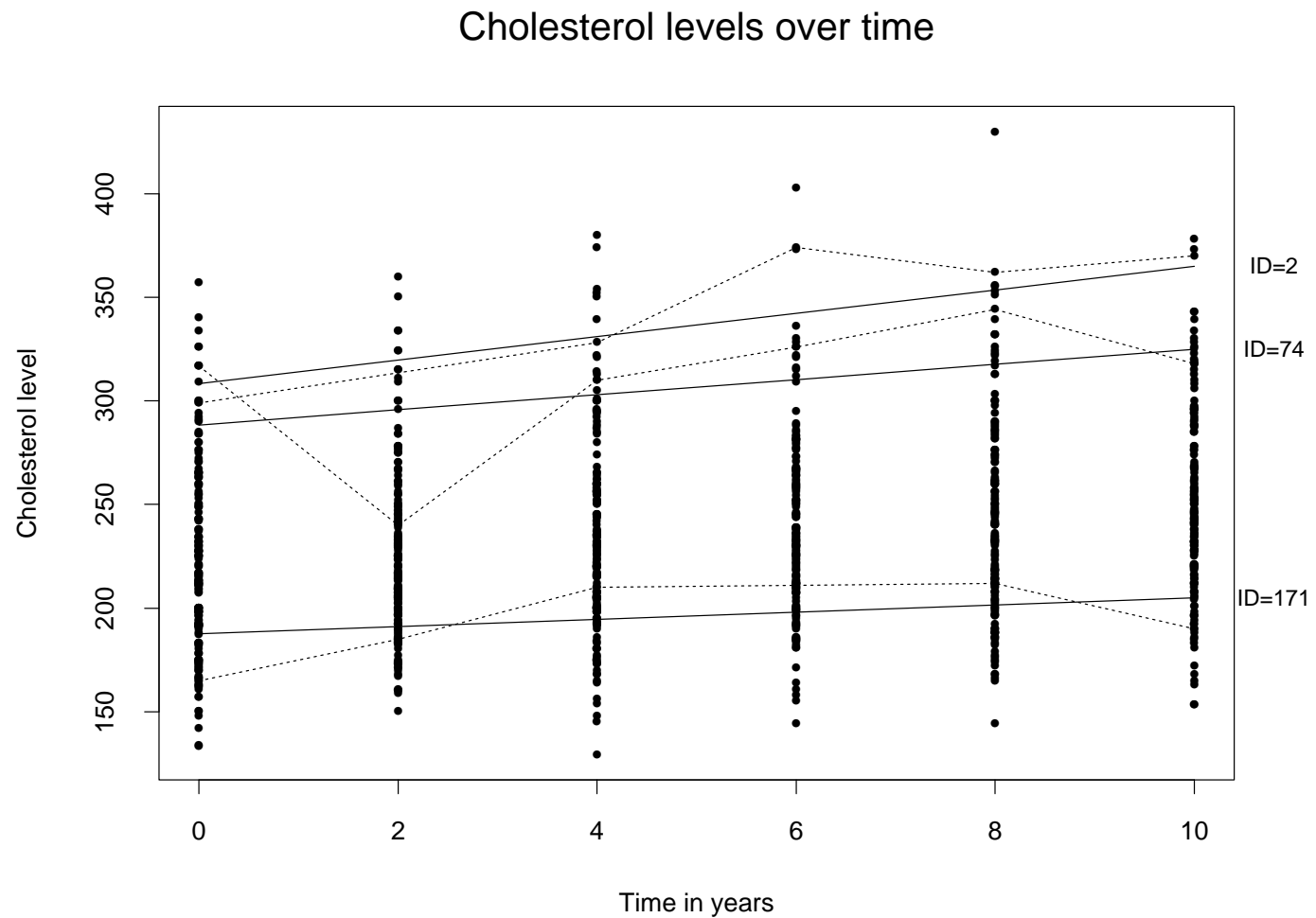
- Model to address Objective 3: Do males have more stable (true) baseline cholesterol level and change rate than females?

    ⋆ From model (2.1), assume b_{i0}^*, b_{i1}^* have different distributions for males and females:

$$\text{Males: } \begin{pmatrix} b_{i0}^* \\ b_{i1}^* \end{pmatrix} \sim N \left(\begin{bmatrix} \mu_{m0} \\ \mu_{m1} \end{bmatrix}, \begin{bmatrix} \sigma_{m00} & \sigma_{m01} \\ \sigma_{m01} & \sigma_{m11} \end{bmatrix} \right)$$

$$\text{Females: } \begin{pmatrix} b_{i0}^* \\ b_{i1}^* \end{pmatrix} \sim N \left(\begin{bmatrix} \mu_{f0} \\ \mu_{f1} \end{bmatrix}, \begin{bmatrix} \sigma_{f00} & \sigma_{f01} \\ \sigma_{f01} & \sigma_{f11} \end{bmatrix} \right) \quad (2.9)$$

    ⋆ We would like to test

    $\text{H}_0 : \sigma_{m00} = \sigma_{f00}, \sigma_{m01} = \sigma_{f01}, \sigma_{m11} = \sigma_{f11}$ (i.e., the above two variance-covariance matrices are the same).

⋆ The SAS program and its output for fitting above model are as follows:

```
data cholst; set cholst;
  gender=sex;
run;

title "Framingham data: do males have more stable (true) baseline";
title2 "cholesterol level and change rate than females?";
proc mixed data=cholst;
  class newid gender;
  model cholst = sex time sex*time / s;
  random intercept time / type=un subject=newid group=gender g;
  repeated / type=vc subject=newid;
run;
```

```
              Framingham data: do males have more stable (true) baseline        1
                    cholesterol level and change rate than females?

                              The Mixed Procedure


                                 Iteration History

        Iteration      Evaluations      -2 Res Log Like          Criterion

                0                1         10889.09479529
                1                3          9939.57691271         0.00000317
                2                1          9939.56399905         0.00000000

                            The Mixed Procedure

                        Convergence criteria met.
```

Estimated G Matrix

Row	Effect	newid	gender	Col1	Col2	Col3	Col4
1	Intercept	1	0	1402.47	-4.7015		
2	time	1	0	-4.7015	1.8279		
3	Intercept	1	1			1532.81	3.6119
4	time	1	1			3.6119	4.7970

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
UN(1,1)	newid	gender 0	1402.47
UN(2,1)	newid	gender 0	-4.7015
UN(2,2)	newid	gender 0	1.8279
UN(1,1)	newid	gender 1	1532.81
UN(2,1)	newid	gender 1	3.6119
UN(2,2)	newid	gender 1	4.7970
Residual	newid		433.71

Fit Statistics

-2 Res Log Likelihood	9939.6
AIC (smaller is better)	9953.6
AICC (smaller is better)	9953.7
BIC (smaller is better)	9976.7

⋆ In order to test H_0 : the two variance matrices are the same using the likelihood ratio test (LRT), we need to fit a model with the same fixed and random effects but under H_0. The following is the SAS program and its output under H_0. This null model is called model (2.9_0).

```
title "Framingham data under H0: males and females have the same variance";
title2 "matrices of baseline cholesterol level and change rate";
proc mixed data=cholst;
  class newid gender;
  model cholst = sex time sex*time / s;
  random intercept time / type=un subject=newid g;
  repeated / type=vc subject=newid;
run;
```

```
   Framingham data under H0: males and females have the same variance    1
           matrices of baseline cholesterol level and change rate

                          The Mixed Procedure

                         Model Information

             Data Set                      WORK.CHOLST
             Dependent Variable            cholst
             Covariance Structures         Unstructured, Variance




                          The Mixed Procedure

                     Convergence criteria met.
```

```
                       Estimated G Matrix

        Row     Effect         newid         Col1          Col2

          1     Intercept        1          1465.85       -0.2516
          2     time             1          -0.2516        3.2618


                 Covariance Parameter Estimates

             Cov Parm         Subject      Estimate

             UN(1,1)          newid         1465.85
             UN(2,1)          newid         -0.2516
             UN(2,2)          newid          3.2618
             Residual         newid         434.17



                         Fit Statistics

           -2 Res Log Likelihood              9943.0
           AIC (smaller is better)            9951.0
           AICC (smaller is better)           9951.1
           BIC (smaller is better)            9964.2
```

⋆ The difference of -2 residual log likelihood is 9943 -
9939.6 = 3.4 (between models (2.9) and (2.9$_0$)) and the P-value
= $P[\chi^2_3 \geq 3.4] = 0.33$.

⋆ **Note**: We can also test H_0: *whether or not males and females have the same variance matrices of true baseline cholesterol level and change rate of cholesterol level* by adjusting for baseline age and sex. We already fit the model under H_0 (model (2.8)) and `-2 residual log likelihood` is 9907.9. The alternative model can be fit using the following SAS program (called model (2.8_A)).

```
title "Framingham data: do males have more stable (true) baseline cholesterol";
title2 "level and change rate than females adjusting for sex and baseline age";
proc mixed data=cholst;
  class newid gender;
  model cholst = sex age time sex*time age*time / s;
  random intercept time / type=un subject=newid group=gender g;
  repeated / type=vc subject=newid;
run;
```

⋆ Part of the output from above program is

Framingham data: do males have more stable (true) baseline cholester 20
level and change rate than females adjusting for sex and baseline age

The Mixed Procedure

Model Information

```
Data Set                        WORK.CHOLST
Dependent Variable              cholst
Covariance Structures           Unstructured, Variance
```

The Mixed Procedure

Convergence criteria met.

Estimated G Matrix

Row	Effect	newid	gender	Col1	Col2	Col3	Col4
1	Intercept	1	0	1403.04	-2.6077		
2	time	1	0	-2.6077	1.5955		
3	Intercept	1	1			1021.77	30.7768
4	time	1	1			30.7768	3.3214

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
UN(1,1)	newid	gender 0	1403.04
UN(2,1)	newid	gender 0	-2.6077
UN(2,2)	newid	gender 0	1.5955
UN(1,1)	newid	gender 1	1021.77

```
UN(2,1)        newid        gender 1        30.7768
UN(2,2)        newid        gender 1         3.3214
Residual       newid                         434.93
```

```
                    Fit Statistics

    -2 Res Log Likelihood              9901.6
    AIC (smaller is better)            9915.6
    AICC (smaller is better)           9915.7
    BIC (smaller is better)            9938.7
```

⋆ The -2 residual log likelihood is 9901.6 so difference is 9907.9-9901.6 = 6.3. The P-value = $P[\chi^2_3 \geq 6.3] = 0.09$, more evidence against H_0.

Comparison of fit statistics among models

Model	AIC	BIC
Model (2.1)	9968.1	9981.3
Model (2.5)	9937.	9950.9
Model (2.8)	9915.9	9929.1
Model (2.9)	9953.6	9976.7
Model (2.9_0)	9951.0	9964.2
Model (2.8_A)	9915.6	9938.7

- **Note**:

  1. The choice of model, especially the fixed effects terms, depends on the questions we need to answer. However, we can use AIC or BIC to determine the random effects and the error structure.

  2. If we want a model with the most prediction power, we can consider a complicated model with AIC or BIC as a guide for model selection.

  3. It seems that model (2.8) is the winner among the above models if we are looking for a model with the most prediction power.

2.5 GEE for linear mixed models

- When the variation pattern in data is so complicated that we don't feel comfortable in the random effects and their variance structure we imposed, we can use the model we posed to estimate the fixed effects (β's) and use the GEE approach to calculate the SEs for the fixed effect estimates. These SE estimates will be valid regardless of the validity of the random effects structure we put. So these SE estimates are robust (we will talk more on Thursday).

- For example, we can use the following model to estimate β's:

$$
\begin{aligned}
y_{ij} = {} & \beta_0 + \beta_1 t_{ij} + \beta_2 \text{sex}_i + \beta_3 \text{age}_i + \beta_4 \text{sex}_i t_{ij} + \beta_5 \text{age}_i t_{ij} \\
& + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}.
\end{aligned}
$$

If we specify `empirical` in `Proc mixed`, we will get robust SE estimates. See the following SAS program and output.

```
title "Using GEE to fit Framingham data";
proc mixed data=cholst empirical;
  class newid;
  model cholst = time sex age sex*time age*time / s;
  random intercept time / type=un subject=newid;
  repeated / type=vc subject=newid;
run;
```

Output of the above program

<pre>
                    Using GEE to fit Framingham data   24

                           The Mixed Procedure

                            Model Information

        Data Set   WORK.CHOLST
        Dependent Variable   cholst
        Covariance Structures   Unstructured, Variance
                                    Components
        Subject Effects   newid, newid
        Estimation Method   REML
        Residual Variance Method   Parameter
        Fixed Effects SE Method   Empirical
        Degrees of Freedom Method   Containment

                           Iteration History

     Iteration   Evaluations   -2 Res Log Like   Criterion

             0   1   10813.99587154
             1   2   9907.89014721   0.00000655
             2   1   9907.86364103   0.00000000

                       Convergence criteria met.
</pre>

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Estimate
UN(1,1)	newid	1209.89
UN(2,1)	newid	13.5502
UN(2,2)	newid	2.5211
Residual	newid	434.15

Fit Statistics

-2 Res Log Likelihood	9907.9
AIC (smaller is better)	9915.9
AICC (smaller is better)	9915.9
BIC (smaller is better)	9929.1

Null Model Likelihood Ratio Test

DF	Chi-Square	Pr > ChiSq
3	906.13	<.0001

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	138.18	15.4017	197	8.97	<.0001
sex	-9.6393	5.4588	651	-1.77	0.0779
age	2.0509	0.3749	651	5.47	<.0001
time	6.8003	1.2188	190	5.58	<.0001
time*sex	1.7995	0.4524	651	3.98	<.0001
time*age	-0.1145	0.02868	651	-3.99	<.0001

What we observed:

1. Fixed effects estimates and variance-covariance parameter estimates are exactly the same as those from model (2.8).

2. The SEs for the fixed effects estimates are different from those from model (2.8). However, they are very close, indicating model (2.8) has a reasonably good fit to the data and we don't have to use the GEE approach.

2.6 Missing data issues

However, GEE will be less efficient if a correct model can be specified; with missing data, the missing data mechanism has to be *missing completely at random* (MCAR) for the GEE inference to be valid.

Missing data mechanism:

1. *missing completely at random* (MCAR): The reason that the data are missing has nothing to do with anything, i.e., at each time point, the observed data can be viewed as a random sample from the population.

2. *missing at random* (MAR): The reason that a subject has missing data does not depend on his/her un-observed data. Mixed model inference is valid under this condition. MCAR implies MAR.

3. *missing not at random* (MNAR): The reason that a subject has missing data depends on his/her unobserved data. Special assumption (untestable) has to be made for inference.

Ways to assess MCAR

1. Suppose the missing data pattern (for y) looks like

<div align="center">

Time points

1   2   3

</div>

and assume x (such as age) is a completely observed variable.

2. Compare x for the two groups with observed y and missing y at times 2 and 3 (using, say, two-sample t-test). A significant difference indicates the violation of MCAR. Otherwise, you may feel comfortable about the MCAR assumption.

Remark: MAR cannot be tested.

Use age to test MCAR for Framingham data:

```
options ls=72 ps=72;

data cholst;
   infile "cholst.dat";
   input newid id cholst sex age time;
   if time = . then delete;
run;

data base; set cholst;
   if time=0;
   keep newid age;
run;

data time;
   do newid=1 to 200;
      do time=0 to 10 by 2;
         output;
      end;
   end;
run;

data cholst; merge cholst time;
   by newid time;
   if cholst=. then yobs=0;
   else yobs=1;
   drop age;
run;

data cholst; merge cholst base;
   by newid;
run;

proc sort;
   by time;
run;
```

```
title "Test equality of age between missing and non-missing groups";
proc ttest;
   var age;
   class yobs;
   by time;
run;
```

SAS output:

Test equality of age between missing and non-missing groups   1

---------------------------- time=2 -----------------------------

The TTEST Procedure

T-Tests

Variable	Method	Variances	DF	t Value	Pr > |t|
age	Pooled	Equal	198	0.35	0.7298
age	Satterthwaite	Unequal	29.6	0.35	0.7325

---------------------------- time=4 -----------------------------

The TTEST Procedure

T-Tests

Variable	Method	Variances	DF	t Value	Pr > |t|
age	Pooled	Equal	198	-0.23	0.8172
age	Satterthwaite	Unequal	39.5	-0.22	0.8304

```
---------------------------- time=6 ----------------------------------

                            T-Tests

    Variable      Method             Variances      DF     t Value     Pr > |t|

    age           Pooled             Equal          198       1.43       0.1536
    age           Satterthwaite      Unequal        40.3      1.37       0.1774


---------------------------- time=8 ----------------------------------

                            T-Tests

    Variable      Method             Variances      DF     t Value     Pr > |t|

    age           Pooled             Equal          198       0.47       0.6418
    age           Satterthwaite      Unequal        47        0.50       0.6179


---------------------------- time=10 ----------------------------------

                            T-Tests

    Variable      Method             Variances      DF     t Value     Pr > |t|

    age           Pooled             Equal          198       0.24       0.8071
    age           Satterthwaite      Unequal        63.3      0.27       0.7879
```

3   Modeling and design issues

- How to handle baseline response?

- Do we model previous responses as covariates?

- Modeling response vs. modeling the change of response

- A simulation study comparing modeling response to modeling its change

- Design a longitudinal study. Sample size calculation
  1. Comparing time-averaged means
  2. Comparing slopes

3.1   How to handle baseline response?

- Model baseline outcome as part of the response. For example,

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \epsilon_{ij}, \qquad i = 1, ..., m, j = 1, 2, ..., n_i, \qquad (3.1)$$

  where the errors ϵ_{ij} include random effects and other errors, and hence are correlated. For example, $\epsilon_{ij} = b_i + \varepsilon_{ij}$ for a random intercept model.

- Model baseline outcome as a covariate. For example,

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \beta_2 y_{i1} + e_{ij}, \qquad i = 1, ..., m, j = 2, ..., n_i. \quad (3.2)$$

Comments:

1. There are some subtle difference between these two models. The regression parameters β_0, β_1 and the variance components have different interpretation and hence we will get different estimates from two models. β_1 in model (3.1) is the overall effect of x on y,

while β_1 in model (3.2) is the adjusted covariate effect of x on y adjusting for baseline response.

2. Model (3.2) is more convenient for prediction. Although one can also get a prediction model similar to model (3.2) by conditioning on the baseline response from model (3.1).

3. When baseline response y_{i1} is used as a covariate, it CANNOT be re-used in the outcome variable. For model (3.2), index j goes from 2 to n_i. Because of this, the estimates from model (3.1) may be more efficient.

4. It is obvious that in the presence of missing data, the subjects with baseline measurements only will be deleted from analysis if model (3.2) is used. In the case where missingness depends on the baseline measurements, inference using model (3.2) will be invalid. However, model (3.1) will still give valid inference. We will see a simulation study later.

3.2   Do we model previous responses as covariates?

One might consider an auto-regressive type of model like the following one instead of (3.1):

$$y_{ij} = \beta_0 + \beta_1 x_{ij} + \beta_2 y_{i,j-1} + \epsilon_{ij}, \qquad i = 1, ..., m, j = 2, ..., n_i. \quad (3.3)$$

Comments:

1. This model is different from models (3.1) and (3.2). Here β_1 is the adjusted effect of x on y after adjusting for the previous response. Therefore, they have different interpretation.

2. Since we allow the current response depends on the previous response in this model, part of the correlation among responses is taken away by the coefficient β_2. Hence the errors may have much simpler variance structure than the errors in model (3.1). In fact, people often assume ϵ_{ij} in (3.3) to be independent. This is an

example of **transition** models. Consequently, the variance component parameters in this model are different and have different interpretation from those in model (3.1).

3. We can obtain a similar model to this one if we assume the errors in model (3.1) have an AR(1) variance structure.

4. Similar to model (3.2), this model is more convenient for prediction.

5. Similar to model (3.2), subjects with baseline measurements only will be deleted from the analysis. If missingness of subsequent measurements depends on the baseline measurements, this model will give invalid inference on the parameters of interest.

3.3 Modeling outcome vs. modeling the change of outcome

Define change from baseline:

$$D_{ij} = y_{ij} - y_{i1}, \qquad i = 1, ..., m, j = 2, ..., n_i$$

and consider model

$$D_{ij} = \beta_0 + \beta_1 x_{ij} + \epsilon_{ij}, \qquad i = 1, ..., m, j = 2, ..., n_i. \tag{3.4}$$

Comments:

1. This model emphasizes the effect of x on the change (from baseline value) of outcome. Therefore, β_1 has different interpretation than the β_1's in previous models.

2. Since we are modeling the difference, part of the correlation in the responses due to among individual variation is removed. Therefore, the errors in this model will have a simpler variance structure than

model (3.1), and the parameters in the variance structures have different interpretation.

3. Baseline outcome y_{i1} can be used as a covariate.

4. It cannot model how x affects the overall mean of outcome.

5. Similar to models (3.2) and (3.3), subjects with baseline measurements only will be deleted from the analysis, and if missingness depends on the baseline measurements, the inference will be invalid.

6. Which model to use depends on the scientific questions we want to address.

A simulation study

We generated data from the following model:

$$y_{ij} = \beta_0 + \beta_1 t_j + b_i + \varepsilon_{ij}, \qquad i = 1, ..., 50, \qquad j = 1, 2,$$

where $\beta_0 = 1$, $\beta_1 = 2$, $t_1 = 0, t_2 = 1$, $b_i \sim N(0, 1)$, $\varepsilon_{ij} \sim N(0, 1)$.

1. y_{i1} can be viewed as pre-test (or baseline) score, y_{i2} can be viewed as post-test score for subject i.

2. In the simulation, we let y_{i2} be missing whenever the baseline measurement y_{i1} is negative.

3. $\beta_1 = \mathrm{E}(y_{i2}) - \mathrm{E}(y_{i1})$. We would like to make inference on β_1 in the presence of missing data.

One simulated data set:

Obs	id	score0	score1	scoredif
1	1	1.33662	1.96479	0.62816
2	2	0.17404	1.93052	1.75648
3	3	1.45672	5.07021	3.61349
4	4	1.08229	3.71837	2.63608
5	5	0.55392	2.51172	1.95780
6	6	1.73579	3.43906	1.70327
7	7	-0.27640	.	.
8	8	0.78154	1.60275	0.82121
9	9	-0.33015	.	.
10	10	-1.11409	.	.
11	11	1.54039	2.02123	0.48084
12	12	1.20696	2.19839	0.99143
13	13	1.35767	2.33060	0.97293
14	14	0.68858	1.55404	0.86545
15	15	0.81951	3.78494	2.96542
16	16	0.49849	1.40747	0.90897
17	17	-1.68078	.	.
18	18	2.31063	3.70494	1.39431
19	19	1.05800	2.22613	1.16813
20	20	1.00388	4.72160	3.71773
21	21	4.45060	7.63933	3.18873
22	22	2.20755	2.18365	-0.02390
23	23	1.02019	1.81962	0.79943
24	24	2.30880	4.09571	1.78691
25	25	1.93793	3.26014	1.32222
26	26	-1.30937	.	.
27	27	-0.80651	.	.
28	28	0.65134	4.66953	4.01819
29	29	0.72529	0.77726	0.05197
30	30	1.00030	4.76540	3.76511
31	31	2.75257	5.03208	2.27951
32	32	-1.71925	.	.
33	33	0.65070	3.11335	2.46265
34	34	0.23703	2.03079	1.79376
35	35	-1.32099	.	.

```
36      36       0.50320      1.96533      1.46214
37      37       4.41193      5.55117      1.13924
38      38      -0.60138         .            .
39      39      -0.24154         .            .
40      40       2.31534      3.74849      1.43315
41      41       1.55065      5.14498      3.59433
42      42       1.32359      5.46448      4.14089
43      43       1.08330      4.74553      3.66223
44      44       0.14231      3.23607      3.09376
45      45      -0.08897         .            .
46      46      -1.03434         .            .
47      47       3.75676      4.16679      0.41004
48      48       3.19876      4.32866      1.12990
49      49       1.02650      2.97035      1.94386
50      50       1.39603      1.75847      0.36244
```

1. If we take difference as we did in the previous model, then we would use the sample mean of the non-missing difference (only 38 differences) to estimate β_1, this will give $\widehat{\beta}_1 = 1.85$ (SE=0.20). Obviously, this estimate is biased (here it is biased towards zero). This is a special case of two-stage analyses.

2. Since we have a special case of longitudinal studies, we can use mixed model approach to estimate β_1. For this purpose, let us re-arrange data in the right format for `Proc mixed`.

3. The data for the first 20 subjects are given below:

```
Obs     id        score       time

 1       1       1.33662        0
 2       1       1.96479        1
 3       2       0.17404        0
 4       2       1.93052        1
 5       3       1.45672        0
 6       3       5.07021        1
 7       4       1.08229        0
 8       4       3.71837        1
 9       5       0.55392        0
10       5       2.51172        1
11       6       1.73579        0
12       6       3.43906        1
13       7      -0.27640        0
14       7          .           1
15       8       0.78154        0
16       8       1.60275        1
17       9      -0.33015        0
18       9          .           1
19      10      -1.11409        0
20      10          .           1
```

4. We use the following SAS program for estimating β_1

```
proc mixed data=maindat;
  class id;
  model score = time / s;
  random int / subject=id type=vc;
  repeated / subject=id type=vc;
run;
```

5. Part of the output from the above SAS program:

```
                     The Mixed Procedure

                      Model Information

    Data Set                       WORK.MAINDAT
    Dependent Variable             score
    Covariance Structure           Variance Components
    Subject Effects                id, id
    Estimation Method              REML
    Residual Variance Method       Parameter
    Fixed Effects SE Method        Model-Based
    Degrees of Freedom Method      Containment


                  Class Level Information

       Class     Levels     Values

       id            50     1 2 ..

                        Dimensions

            Covariance Parameters            2
            Columns in X                     2
            Columns in Z Per Subject         1
            Subjects                        50
            Max Obs Per Subject              2
            Observations Used               88
            Observations Not Used           12
            Total Observations             100

                Convergence criteria met.


              Covariance Parameter Estimates
```

```
             Cov Parm        Subject      Estimate

             Intercept         id          1.4573
             Residual          id          0.7828


                   Fit Statistics

        -2 Res Log Likelihood             300.6
        AIC (smaller is better)           304.6
        AICC (smaller is better)          304.8
        BIC (smaller is better)           308.4
```

The SAS System   5

The Mixed Procedure

Solution for Fixed Effects

```
                        Standard
Effect        Estimate      Error        DF     t Value     Pr > |t|

Intercept      0.9146      0.2117        49       4.32       <.0001
time           2.0503      0.1987        37      10.32       <.0001
```

Type 3 Tests of Fixed Effects

```
                    Num      Den
         Effect      DF       DF     F Value     Pr > F

         time         1       37     106.50      <.0001
```

- The following table gives the simulation results comparing the longitudinal approach modeling all responses simultaneously and the two-stage approach modeling the difference based on 1000 simulation runs:

Method	Mean	SE	SD	Cov. prob.
Longitudinal approach	2.002	0.222	0.257	0.91
Two-stage approach	1.712	0.214	0.217	0.72

where **Mean** is the sample mean of 1000 $\widehat{\beta}_1$'s from both approaches; **SE** is the sample mean of 1000 estimated SEs of $\widehat{\beta}_1$; **SD** is the sample standard deviation of 1000 $\widehat{\beta}_1$'s; **Cov. prob.** is the empirical coverage probability of 95% CI of β_1.

What we see from this table:

1. The estimate $\widehat{\beta}_1$ using longitudinal approach by modeling all responses simultaneously is unbiased; however, if we take difference of the responses (here we are forced to delete all subjects with missing measurements), the estimate $\widehat{\beta}_1$ is biased.

2. Although the estimate $\widehat{\beta}_1$ from the two-stage approach has slightly smaller SE or SD, since the estimate itself is biased, the coverage probability of the 95% CI of β_1 is too low, making invalid inference on β_1. However, the coverage probability of the 95% CI of β_1 from the longitudinal approach is almost right at the nominal level (0.95).

3. With mixed model approach, we can estimate other quantities.

3.4 Design a longitudinal study: Sample size estimation

Recall that in the classical setting, sample size estimation is posed as a hypothesis testing problem such as the following one

$$H_0 : \mu_1 = \mu_2 \quad vs \quad H_A : \mu_1 \neq \mu_2.$$

Assume $y_{1k}, ..., y_{mk} \sim N(\mu_k, \sigma^2), k = 1, 2$. Given significance level α, power γ, and the difference $\Delta = (\mu_1 - \mu_2)/\sigma$ we wish to detect, the required total sample size (number of subjects) in each group should be

$$m = 2 \left[\frac{z_{\alpha/2} + z_{1-\gamma}}{\Delta} \right]^2.$$

Design a longitudinal study (cont'd):

I: Compare time-averaged means between two groups.

Assume model for the data to be collected:

$$\text{Group A} : y_{ij} = \mu_A + \varepsilon_{ij}, i = 1, ..., m, j = 1, ..., n$$
$$\text{Group B} : y_{ij} = \mu_B + \varepsilon_{ij}, i = 1, ..., m, j = 1, ..., n$$

$m = \#$ of subjects, $n = \#$ of observations/subject, ε_{ij} normally distributed errors with mean zero, variance σ^2 and correlation ρ.

We want to test

$$H_0 : \mu_A = \mu_B \quad vs \quad H_A : \mu_A \neq \mu_B$$

at level α with power γ to detect difference $\Delta = (\mu_A - \mu_B)/\sigma$. The quantities m and n have to satisfy

$$m = 2(1 + (n-1)\rho)\frac{(z_{\alpha/2} + z_{1-\gamma})^2}{n\Delta^2}.$$

Comments:

1. When $n = 1$, the study reduces to a cross-sectional study and the sample size formula reduces to the classical one.

2. When $\rho = 0$ (responses are independent), the required sample size is $1/n$ of that for classical study.

3. When $\rho = 1$, required sample size is the same as that of the classical study.

4. For fixed n, smaller ρ gives smaller sample size.

5. If correlation is high, use more subjects and less obs/subject; if correlation is low, use less subjects and more obs/subject.

6. The sample size formula depends on information on σ^2 and ρ.

7. One can choose a combination of m and n to meet one's specific needs.

8. The above formula is for two-sided test.

- An example: If $n = 3, \alpha = 0.05, \gamma = 0.8$, then the number of subjects (m) per group is

$$m = 2(1 + 2\rho)\frac{(1.96 + 0.84)^2}{3\Delta^2}$$

ρ	Δ							
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8
0.2	733	184	82	46	30	21	15	12
0.3	838	210	94	53	34	24	18	14
0.4	942	236	105	59	38	27	20	15
0.5	1047	262	117	66	42	30	22	17
0.6	1152	288	128	72	47	32	24	18
0.7	1256	314	140	79	51	35	26	20
0.8	1361	341	152	86	55	38	28	22

Design a longitudinal study (cont'd):

II: Compare slopes between two groups.

Model for the data to be collected:

$$\text{Group A}: y_{ij} = \beta_{0A} + \beta_{1A}t_j + \varepsilon_{ij}, i = 1, ..., m, j = 1, ..., n$$

$$\text{Group B}: y_{ij} = \beta_{0B} + \beta_{1B}t_j + \varepsilon_{ij}, i = 1, ..., m, j = 1, ..., n$$

$m = \#$ of subjects, $n = \#$ of observations/subject, ε_{ij} are normal errors with mean zero, variance σ^2 and correlation ρ.

We are interested in testing

$$H_0 : \beta_{1A} = \beta_{1B} \quad vs \quad H_A : \beta_{1A} \neq \beta_{1B}$$

at level α with power γ to detect difference $\Delta = (\beta_{1A} - \beta_{1B})/\sigma$. The quantities m and n have to satisfy

$$m = \frac{2(1 - \rho)(z_{\alpha/2} + z_{1-\gamma})^2}{n\Delta^2 s_t^2}, \quad s_t^2 = \frac{\sum_{j=1}^{n}(t_j - \bar{t})^2}{n}.$$

Comments:

1. For fixed time points t_j, larger ρ gives smaller sample size m.

2. If $\rho = 1$, one subject from each group is enough.

3. $\rho = 0$ will require maximum sample size m.

4. If correlation is low, use more subjects and less obs/subject; if correlation is high, use less subjects and more obs/subject.

5. The sample size formula depends on information on σ^2 and ρ and the placement of time points t_j's.

6. One can choose a combination of m and n to meet one's specific needs.

7. The above formula is for two-sided test.

- An example: If $n = 3, \alpha = 0.05, \gamma = 0.8, t = (0, 2, 5)$ so $s_t^2 = 4.222$, then the number of subjects (m) per group is

$$m = \frac{2(1 - \rho)(1.96 + 0.84)^2}{3 \times 4.222\Delta^2}$$

| | Δ | | | | | | | | |
ρ	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.10
0.2	2479	1102	620	397	276	203	155	123	100
0.3	2169	964	543	348	241	178	136	108	87
0.4	1859	827	465	298	207	152	117	92	75
0.5	1550	689	388	248	173	127	97	77	62
0.6	1240	551	310	199	138	102	78	62	50
0.7	930	414	233	149	104	76	59	46	38
0.8	620	276	155	100	69	51	39	31	25

4   Modeling discrete longitudinal data

- Generalized estimating equations (GEEs)

  1. Why GEEs?

  2. Key features of GEEs

  3. Some popular GEE models

  4. Some basics of GEEs

  5. Interpretation of GEEs

  6. Analyze infectious disease data using GEE

  7. Analyze epileptic data using GEE

- Generalized linear mixed models (GLMMs)

  1. Model specification & implementation

  2. Analyze infectious disease data using a GLMM

  3. Analyze epileptic data using a GLMM

4.1 Generalized estimating equations (GEEs) for continuous and discrete longitudinal data

4.1.1 Why GEEs?

- Recall that a linear mixed model for longitudinal data may take the form:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 x_{ij2} + \cdots + \beta_p x_{ijp} + b_{i0} + b_{i1} t_{ij} + \varepsilon_{ij}.$$

- **Key features**:

  1. Outcome y_{ij} is continuous and **normally** distributed.

  2. Correlation in outcome observations from the same individuals is directly modeled using random effects (e.g., random intercept and slope).

- **However**,

  1. in many biomedical studies, the outcome variables are discrete

(not continuous). For example, the outcome is binary (yes/no) in Indonesian children study, and the outcome is count in the Epileptic clinical trial.

2. sometimes, we are mainly interested in the covariate effects, not in correlation among the outcome observations from the same subject. A partial reason is that it is much harder to know how the discrete observations are correlated to each other over time than continuous outcomes.

3. we might also want to model the correlation in a natural way jointly with the estimation of covariate effects of interest.

What is wrong with the classical regression approach such as the logistic regression for binary outcomes?

- Classical logistic regression model:

$$y_i \sim \text{Binomial}(1, \pi_i(x_i)), \quad y_i = 1/0, \quad \pi_i(x_i) = \text{E}[y_i | x_i]$$

$$\text{logit}\{\pi_i(x_i)\} = \log\left\{\frac{\pi_i(x_i)}{1 - \pi_i(x_i)}\right\} = \beta_0 + \beta_1 x_{i1} + \cdots + \beta_p x_{ip}.$$

- **Key features**:

  1. Each subject contributes only one binary observation.

  2. It is reasonable to assume that the outcomes from different subjects are **independent**.

- **However, in a longitudinal study**,

  1. Each subject has multiple binary (1/0) responses over time.

  2. The subjects with higher probability to get disease will tend to have more 1's, resulting a correlation.

  3. Even though a classical regression by ignoring correlation will

give us correct and meaningful regression coefficient estimates, their SEs are often too small, resulting invalid inference.

4. The correlation has to be taken into account for valid inference (to get correct standard errors of the regression coefficient estimates).

- **Generalized estimating equations (GEEs)** is an approach that allows us to make valid inference by implicitly taken into account the correlation.

4.1.2   Key features of GEEs for analyzing longitudinal data

1. We only need to **correctly** specify how the mean of the outcome variable is related to the covariates of interest. For example, for the infection disease study,

$$y_{ij} \sim \text{Binomial}\{1, \pi_{ij}(x_{ij})\}$$

$$\text{logit}\{\pi_{ij}(x_{ij})\} = \beta_0 + \beta_1 \text{Xero}_{ij} + \beta_2 \text{sinv}_{ij} + \beta_3 \text{age}_i$$

$$+\beta_4 \text{time}_{ij} + \beta_5 \text{sex}_i + \beta_6 \text{height}_{ij},$$

$\pi_{ij}(x_{ij}) = P[y_{ij} = 1 | x_{ij}] = \text{E}(y_{ij} | x_{ij})$ is the **population probability** of respiratory infection for the population defined by the specific covariate values (i.e., x_{ij}).

2. The correlation among the observations from the same subject over time is not the major interest and is treated as nuisance.

3. We can specify a correlation structure. The validity of the inference does not depend on the whether or not the specification of the

correlation structure is correct. GEE will give us a robust inference on the regression coefficients, which is valid regardless whether or not the correlation structure we specified is right.

4. GEE calculates correct SEs for the regression coefficient estimates using *sandwich* estimates that will take into account the possibility that the correlation structure is misspecified.

5. The regression coefficients in GEE have a population-average interpretation.

6. A fundamental assumption on missing data is that missing data mechanism has to be MCAR, while a likelihood-based approach only requires MAR. The GEE approach will also be less efficient than a likelihood-based approach if the likelihood can be correctly specified.

4.1.3   Some popular GEE Models

- Continuous (Normal):

$$\mu(x) = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p$$

  where $\mu(x) = \mathrm{E}(y|x)$ is the mean of outcome variable at $x = (x_1, ..., x_p)$, such as mean of cholesterol level.

- Proportion (Binomial, Binary):

$$\mathrm{logit}\{\pi(x)\} = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p$$

  $\pi(x) = P[y = 1|x] = \mathrm{E}(y|x)$ such as disease risk. $\mathrm{logit}(\pi) = \log\{\pi/(1-\pi)\}$ is the logit link function. Other link functions are possible.

- Count or rate (Poisson-type)

$$\log\{\lambda(x)\} = \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p$$

$\lambda(x)$ is the rate (e.g. $\lambda(x)$ is the incidence rate of a disease) for the count data (number of events) y over a (time, space) region T such that

$$y|x \sim \text{Poisson}\{\lambda(x)T\}$$

Here $\log(.)$ link is used. Other link functions are possible.

Note: For count data, we have to be concerned about the possible over-dispersion in the data. That is

$$\text{var}(y|x) > \text{E}(y|x).$$

One way to model this phenomenon is to use an over-dispersion parameter ϕ and model the variance-mean relationship as follows:

$$\text{var}(y|x) = \phi\text{E}(y|x).$$

4.1.4   Some basics of GEEs

- Data: y_{ij}, $i = 1, ..., m$, $j = 1, ..., n_i$ with mean

$$\mu_{ij} = \mathrm{E}(y_{ij}|x_{ij}).$$

  Denote

$$y_i = \begin{pmatrix} y_{i1} \\ y_{i2} \\ \vdots \\ y_{in_i} \end{pmatrix}, \quad \mu_i = \begin{pmatrix} \mu_{i1} \\ \mu_{i2} \\ \vdots \\ \mu_{in_i} \end{pmatrix}.$$

- Suppose we correctly specify the mean structure for data y_{ij}:

$$g(\mu_{ij}) = \beta_0 + x_{1ij}\beta_1 + ... + x_{pij}\beta_p,$$

  where $g(\mu)$ is the link function such as the logit function for binary response and the log link for count data.

- A GEE solves the following generalized estimating equation for β (Liang and Zeger, 1986):

$$S_\beta(\alpha, \beta) = \sum_{i=1}^{m} \left(\frac{\partial \mu_i}{\partial \beta} \right)^T V_i^{-1} (y_i - \mu_i) = 0, \qquad (4.1)$$

  where V_i is some matrix (intended to specify for $\mathrm{var}(y_i|x_i)$) and α is the possible parameters in the correlation structure.

- The above estimating equation is **unbiased** no matter what matrix V_i we use as long as the mean structure is right. That is

$$\mathrm{E}[S_\beta(\alpha, \beta)] = 0.$$

- Under some regularity conditions, the solution $\widehat{\beta}$ from the GEE equation (4.1) has asymptotic distribution

$$\widehat{\beta} \stackrel{a}{\sim} \mathrm{N}(\beta, \Sigma),$$

where

$$\Sigma = I_0^{-1} I_1 I_0^{-1}$$

$$I_0 = \sum_{i=1}^{m} D_i^T V_i^{-1} D_i$$

$$I_1 = \sum_{i=1}^{m} D_i^T V_i^{-1} \text{var}(y_i | x_i) V_i^{-1} D_i$$

$$= \sum_{i=1}^{m} D_i^T V_i^{-1} (y_i - \mu_i(\widehat{\beta}))(y_i - \mu_i(\widehat{\beta}))^T V_i^{-1} D_i$$

Σ is called the **empirical**, **robust** or **sandwich** variance estimate.

- If V_i is correctly specified, then $I_1 \approx I_0$ and $\Sigma \approx I_0^{-1}$ (model based). In this case, $\widehat{\beta}$ is the most efficient estimate. Otherwise, $\Sigma \neq I_0^{-1}$.

- V_i, the working variance matrix for y_i (at x_i), can be decomposed as

$$V_i = A_i^{1/2} R_i A_i^{1/2},$$

  where

$$A_i = \begin{pmatrix} \text{var}(y_{i1}|x_{i1}) & 0 & \cdots & 0 \\ 0 & \text{var}(y_{i2}|x_{i2}) & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ 0 & \cdots & 0 & \text{var}(y_{in_i}|x_{in_i}) \end{pmatrix},$$

  and R_i is the correlation structure.

- We may try to specify R_i so that it is close to the "true". This R_i is called the *working correlation matrix* and may be mis-specified.

- Some working correlation structures

1. **Independent**: $R_i(\alpha) = I_{n_i \times n_i}$. No α needs to be estimated.

2. **Exchangeable** (compound symmetric):

$$
R_i =
\begin{bmatrix}
1 & \alpha & \cdots & \alpha \\
\alpha & 1 & \cdots & \alpha \\
\vdots & \vdots & \vdots & \vdots \\
\alpha & \alpha & \cdots & 1
\end{bmatrix}
$$

Let $e_{ij} = y_{ij} - \widehat{\mu}_{ij}$. Since $\mathrm{E}(e_{ij}e_{ik}) = \phi\alpha$ (at true β), $\implies$

$$
\widehat{\alpha} = \frac{1}{(N^* - p - 1)\widehat{\phi}} \sum_{i=1}^{m} \sum_{j<k} e_{ij}e_{ik},
$$

where $N^* = \sum_{i=1}^{m} n_i(n_i - 1)/2$ (total # of pairs), ϕ is usually estimated using the Pearson χ^2.

3. **AR(1)**:

$$
R_i =
\begin{bmatrix}
1 & \alpha & \cdots & \alpha^{n_i-1} \\
\alpha & 1 & \cdots & \alpha^{n_i-2} \\
\vdots & \vdots & \vdots & \vdots \\
\alpha^{n_i-1} & \alpha^{n_i-2} & \cdots & 1
\end{bmatrix}
$$

Since $\mathrm{E}(e_{ij}e_{i,j+1}) = \phi\alpha$ (at true β), $\Longrightarrow$

$$
\widehat{\alpha} = \frac{1}{(N^{**} - p - 1)\widehat{\phi}} \sum_{i=1}^{m} \sum_{j=1}^{n_i-1} e_{ij}e_{i,j+1},
$$

where $N^{**} = \sum_{i=1}^{m}(n_i - 1)$ (total # of adjacent pairs).

4. Many more can be found in SAS.

- **Software**: `Proc Genmod in SAS`

4.1.5 Interpretation of regression coefficients in a GEE Model

- A classical logistic model: $y =$ indicator of lung cancer $\sim \mathrm{Bin}(1, \pi)$

$$\mathrm{logit}(\pi) = \beta_0 + \beta_1 X_E + \beta_2 X_C$$

where

$$X_E = \begin{cases} 1 & \text{exposure} = \text{yes} \\ 0 & \text{exposure} = \text{no} \end{cases} \qquad X_C = \begin{cases} 1 & \text{confounder} = \text{yes} \\ 0 & \text{confounder} = \text{no} \end{cases}$$

For example, $X_E =$ smoking (yes/no), $X_C =$ Age (> 50 vs. ≤ 50). Then

$\beta_1 =$ age-adjusted log(OR) ($\approx$ log(RR)) of lung cancer comparing the population of smokers and the population of non-smokers.

- In general, β_k in a logistic regression can be interpreted as

  $\beta_k = \log(\text{OR})$ of disease under consideration for two populations with covariate values $x_k + 1$ and x_k while other covariates are held fixed.

- The regression coefficients in a GEE logistic model have the same *population-averaged* interpretation as those in a classical logistic model.

- GEE combines information from a sample of subjects to estimate these population-averaged estimates. These will be contrasted with subject-specific regression coefficients later.

4.1.6   Analyze Infectious disease data using GEE

- Data:

  - ★ 275 Indonesian preschool children.

  - ★ Each was followed over 6 consecutive quarters.

  - ★ Outcome = respiratory infection (yes/no)

  - ★ Covariates: Xero (xerophthalmia (yes/no)), season, age, sex, height (height for age)

- GEE logistic model: $y_{ij}(1/0)$ = infection indicator $\sim \text{Bin}(1, \pi_{ij})$,

$$\text{logit}(\pi_{ij}) = \beta_0 + \beta_1 \text{Xero}_{ij} + \beta_2 \text{sinv}_{ij} + \beta_3 \text{age}_i$$
$$+ \beta_4 \text{time}_{ij} + \beta_5 \text{sex}_i + \beta_6 \text{height}_{ij}$$

See the SAS program `indon_gee.sas` and its output `indon_gee.lst` for details.

SAS program: `indon_gee.sas`

```
options ls=72 ps=72;

/*-----------------------------------------------------*/
/*                                                     */
/* Proc Genmod to fit population average (marginal)    */
/* model using GEE approach for the Indonesia children */
/* infection disease data                              */
/*                                                     */
/*-----------------------------------------------------*/

data indon;
   infile "indon.dat";
   input id infect intercept age xero cosv sinv sex height stunted
   visit baseage season visitsq;
   time = age-baseage;
   /* sinv = sin(season*8*atan(1)/4); */
run;

data indon; set indon;
   nobs=_n_;
run;

title "Print the first 20 observations";
proc print data=indon (obs=20);
   var id infect xero sex visit season;
run;

title "Model 1: Use exchangeable working correlation";
proc genmod descending;
 class id;
 model infect = xero sinv baseage time sex height
        / dist=bin link=logit;
 repeated subject=id / type=exch corrw;
run;
```

SAS first uses indep. corr to obtain reg parm est:

Analysis Of Initial Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	-2.4708	0.2122	-2.8867	-2.0549	135.59	<.0001
xero	1	0.6661	0.4343	-0.1852	1.5174	2.35	0.1251
sinv	1	-0.0640	0.1517	-0.3613	0.2333	0.18	0.6730
baseage	1	-0.0335	0.0064	-0.0461	-0.0209	27.22	<.0001
time	1	0.0000	0.0200	-0.0392	0.0392	0.00	0.9999
sex	1	-0.3841	0.2188	-0.8129	0.0448	3.08	0.0792
height	1	-0.0476	0.0207	-0.0882	-0.0070	5.29	0.0215

Actual SAS output from the above program:

Model 1: Use exchangeable working correlation   2

The GENMOD Procedure

Model Information

Data Set	WORK.INDON
Distribution	Binomial
Link Function	Logit
Dependent Variable	infect

Number of Observations Read	1200
Number of Observations Used	1200
Number of Events	107
Number of Trials	1200

                          Class Level Information

      Class   Levels   Values

      id   275   121013 121113 121114 121140 121215 121315 121316
                             121413 121414 121514 121616 121617 121713 121813
                             121913 122013 122113 122114 122170 122214 122315
                             124150 124160 125140 127130 128130 129130 129140
                             131015 131016 131116 131140 131215 131216 131315
                             131417 ...

                             Response Profile

                  Ordered   Total
                    Value   infect   Frequency

                        1   1   107
                        2   0   1093

      PROC GENMOD is modeling the probability that infect='1'.

                          Parameter Information

                    Parameter   Effect

                    Prm1   Intercept
                    Prm2   xero
                    Prm3   season
                    Prm4   baseage
                    Prm5   time
                    Prm6   sex
                    Prm7   height

          Algorithm converged.

GEE Model Information

Correlation Structure   Exchangeable
Subject Effect   id (275 levels)
Number of Clusters   275
Correlation Matrix Dimension   6
Maximum Cluster Size   6
Minimum Cluster Size   1

Algorithm converged.

Working Correlation Matrix

	Col1	Col2	Col3	Col4	Col5	Col6
Row1	1.0000	0.0460	0.0460	0.0460	0.0460	0.0460
Row2	0.0460	1.0000	0.0460	0.0460	0.0460	0.0460
Row3	0.0460	0.0460	1.0000	0.0460	0.0460	0.0460
Row4	0.0460	0.0460	0.0460	1.0000	0.0460	0.0460
Row5	0.0460	0.0460	0.0460	0.0460	1.0000	0.0460
Row6	0.0460	0.0460	0.0460	0.0460	0.0460	1.0000

Exchangeable Working
Correlation

Correlation   0.0459822403

GEE Fit Criteria

QIC   700.6732
QICu   699.4715

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	-2.4592	0.2250	-2.9002	-2.0181	-10.93	<.0001
xero	0.5529	0.4479	-0.3249	1.4308	1.23	0.2170
sinv	-0.0575	0.1146	-0.2822	0.1672	-0.50	0.6158
baseage	-0.0339	0.0062	-0.0460	-0.0218	-5.50	<.0001
time	0.0010	0.0210	-0.0401	0.0421	0.05	0.9614
sex	-0.4000	0.2374	-0.8654	0.0653	-1.68	0.0920
height	-0.0509	0.0262	-0.1024	0.0005	-1.94	0.0524

Some remarks:

- `Proc Genmod` in SAS fits the model using independence correlation structure to get initial parameter estimate and get the estimate of over-dispersion parameter (SAS does not output the initial estimates now). We should read the output under "`Analysis Of GEE Parameter Estimates`", which is valid even if the correlation structure we specified (it is exchangeable here) may not be true.

- Given other characteristics, the odds-ratio of getting respiratory infection between two populations with or without Vitamin A deficiency is estimated to be $e^{0.5529} = 1.74$. If respiratory infection could be viewed as a rare disease, kids with Vitamin A deficiency would be 74% more likely to develop respiratory infection. However, p-value=0.2170 indicates that there is no significant difference in infection risk for these two populations.

4.1.7   Analyze epileptic seizure count data using GEE

- Data:

  - ⋆ 59 patients, 28 in control group, 31 in treatment (progabide) group.

  - ⋆ 5 seizure counts (including baseline) were obtained.

  - ⋆ Covariates: treatment (covariate of interest), age.

- GEE Poisson model: y_{ij} =seizure counts obtained at the jth $(j = 0, 1, ..., 4)$ time point for patient i, $y_{ij} \sim$ over-dispersed Poisson(μ_{ij}), $\mu_{ij} = \mathrm{E}(y_{ij}) = t_{ij}\lambda_{ij}$, where t_{ij} is the length of time from which the seizure count y_{ij} was observed, λ_{ij} is hence the rate to have a seizure. First consider model

$$
\begin{aligned}
\log(\lambda_{ij}) &= \beta_0 + \beta_1 I(j > 0) + \beta_2 \mathrm{trt}_i + \beta_3 \mathrm{trt}_i I(j > 0) \\
\log(\mu_{ij}) &= \log(t_{ij}) + \beta_0 + \beta_1 I(j > 0) + \beta_2 \mathrm{trt}_i + \beta_3 \mathrm{trt}_i I(j > 0)
\end{aligned}
$$

Note that $\log(t_{ij})$ is often called an offset.

- Interpretation of β's:

	log of seizure rate λ	
Group	Before randomization	After randomization
Control (trt=0)	β_0	$\beta_0 + \beta_1$
Treatment (trt=1)	$\beta_0 + \beta_2$	$\beta_0 + \beta_1 + \beta_2 + \beta_3$

Therefore, β_1 = time effect, β_2 = difference in seizure rates at baseline between two groups, β_3 = treatment effect of interest.

If randomization is taken into account $(\beta_2 = 0)$, we can consider the following model

$$\log(\mu_{ij}) \quad = \quad \log(t_{ij}) + \beta_0 + \beta_1 I(j > 0) + \beta_2 \mathrm{trt}_i I(j > 0)$$

- See the SAS program `seize_gee.sas` and its output `seize_gee.lst` for details.

First part of `seize_gee.sas`

```
options ls=80 ps=1000 nodate;

/*-----------------------------------------------------*/
/*                                                     */
/* Proc Genmod to fit population average (marginal)    */
/* model using GEE approach for the epileptic seizure  */
/* count data                                          */
/*                                                     */
/*-----------------------------------------------------*/

data seizure;
  infile "seize.dat";
  input id seize visit trt age;
  nobs=_n_;
  interval = 2;
  if visit=0 then interval=8;
  logtime = log(interval);
  assign = (visit>0);
run;


title "Model 1: overall effect of the treatment";
proc genmod data=seizure;
  class id;
  model seize = assign trt assign*trt
     / dist=poisson link=log offset=logtime;
  repeated subject=id / type=exch corrw;
run;
```

SAS first uses indep corr to get reg. coeff est.

Analysis Of Initial Parameter Estimates

Parameter	DF	Estimate	Standard Error	Wald 95% Confidence Limits		Chi-Square	Pr > ChiSq
Intercept	1	1.3476	0.0341	1.2809	1.4144	1565.44	<.0001
assign	1	0.1108	0.0469	0.0189	0.2027	5.58	0.0181
trt	1	0.0265	0.0467	-0.0650	0.1180	0.32	0.5702
assign*trt	1	-0.1037	0.0651	-0.2312	0.0238	2.54	0.1110

Actual SAS output from the above program:

Model 1: overall effct of the treatment   1

The GENMOD Procedure

Model Information

Data Set	WORK.SEIZURE
Distribution	Poisson
Link Function	Log
Dependent Variable	seize
Offset Variable	logtime

Number of Observations Read   295
Number of Observations Used   295

Class Level Information

Class	Levels	Values
id	59	101 102 103 104 106 107 108 110 111 112 113 114 116 117 118 121 122 123 124 126 128 129 130 135

```
137 139 141 143 145 147 201 202 203 204 205 206
207 208 209 210 211 213 214 215 217 218 219 220
221 222 225 226 227 228 230 232 234 236 238
```

Parameter Information

Parameter	Effect
Prm1	Intercept
Prm2	assign
Prm3	trt
Prm4	assign*trt

Algorithm converged.

GEE Model Information

Correlation Structure	Exchangeable
Subject Effect	id (59 levels)
Number of Clusters	59
Correlation Matrix Dimension	5
Maximum Cluster Size	5
Minimum Cluster Size	5

Algorithm converged.

Working Correlation Matrix

	Col1	Col2	Col3	Col4	Col5
Row1	1.0000	0.7716	0.7716	0.7716	0.7716
Row2	0.7716	1.0000	0.7716	0.7716	0.7716
Row3	0.7716	0.7716	1.0000	0.7716	0.7716
Row4	0.7716	0.7716	0.7716	1.0000	0.7716
Row5	0.7716	0.7716	0.7716	0.7716	1.0000

Exchangeable Working
Correlation

Correlation   0.7715879669

GEE Fit Criteria

```
QIC              -659.5869
QICu             -668.6570
```

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	1.3476	0.1574	1.0392	1.6560	8.56	<.0001
assign	0.1108	0.1161	-0.1168	0.3383	0.95	0.3399
trt	0.0265	0.2219	-0.4083	0.4613	0.12	0.9049
assign*trt	-0.1037	0.2136	-0.5223	0.3150	-0.49	0.6274

Second part of `seize_gee.sas`

```
title "Model 2: take randomization into account";
proc genmod data=seizure;
   class id;
   model seize = assign assign*trt
      / dist=poisson link=log offset=logtime scale=pearson aggregate=nobs;
   repeated subject=id / type=exch corrw;
run;
```

Output from the above program:

Model 2: take randomization into account   2

Algorithm converged.

Working Correlation Matrix

	Col1	Col2	Col3	Col4	Col5
Row1	1.0000	0.7750	0.7750	0.7750	0.7750
Row2	0.7750	1.0000	0.7750	0.7750	0.7750
Row3	0.7750	0.7750	1.0000	0.7750	0.7750
Row4	0.7750	0.7750	0.7750	1.0000	0.7750
Row5	0.7750	0.7750	0.7750	0.7750	1.0000

Exchangeable Working
Correlation

Correlation   0.7749556223

GEE Fit Criteria

QIC   -667.9355
QICu   -672.7671

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Parameter						
Intercept	1.3616	0.1111	1.1438	1.5794	12.25	<.0001
assign	0.1173	0.1283	-0.1341	0.3688	0.91	0.3604
assign*trt	-0.1170	0.2076	-0.5240	0.2900	-0.56	0.5731

A program to adjust for age

```
title "Model 3: adjusting for other covariates (age)";
proc genmod data=seizure;
   class id;
   model seize = assign trt assign*trt age
      / dist=poisson link=log offset=logtime scale=pearson;
   repeated subject=id / type=exch corrw;
run;
```

Output of the program to adjust for all covariates

Model 3: adjusting for other covariates   3

Algorithm converged.

Working Correlation Matrix

	Col1	Col2	Col3	Col4	Col5
Row1	1.0000	0.7620	0.7620	0.7620	0.7620
Row2	0.7620	1.0000	0.7620	0.7620	0.7620
Row3	0.7620	0.7620	1.0000	0.7620	0.7620
Row4	0.7620	0.7620	0.7620	1.0000	0.7620
Row5	0.7620	0.7620	0.7620	0.7620	1.0000

Exchangeable Working
Correlation

Correlation   0.7620401547

GEE Fit Criteria

QIC   -686.4053
QICu   -697.2349

Analysis Of GEE Parameter Estimates
Empirical Standard Error Estimates

Parameter	Estimate	Standard Error	95% Confidence Limits		Z	Pr > |Z|
Intercept	2.2601	0.4330	1.4113	3.1088	5.22	<.0001
assign	0.1108	0.1161	-0.1168	0.3383	0.95	0.3399
trt	-0.0175	0.2141	-0.4371	0.4020	-0.08	0.9348
assign*trt	-0.1037	0.2136	-0.5223	0.3150	-0.49	0.6274
age	-0.0321	0.0147	-0.0610	-0.0032	-2.17	0.0296

4.2   Generalized linear mixed models (GLMMs)

4.2.1   Model specification and implementation

- Generalized linear mixed models (GLMMs) are an extension of

  1. linear mixed models (**continuous $\Rightarrow$ discrete**)

  2. logistic (Poisson) models (**independent discrete data $\Rightarrow$ discrete longitudinal data**)

- Consider a special linear mixed model:

$$y_{ij} = \beta_0 + \beta_1 x_{ij1} + \cdots + \beta_p x_{ijp} + b_i + \varepsilon_{ij},$$

where $b_i \sim N(0, \sigma_b^2)$ and $\varepsilon_{ij} \overset{iid}{\sim} N(0, \sigma_\varepsilon^2)$.

Let $\mu_{ij}^b = E[y_{ij}|b_i]$. Then the above model is equivalent to

$$\begin{aligned} y_{ij}|b_i, x_i &\overset{ind}{\sim} N(\mu_{ij}^b, \sigma_\varepsilon^2), \\ \mu_{ij}^b &= \beta_0 + \beta_1 x_{ij1} + \cdots + \beta_p x_{ijp} + b_i. \end{aligned} \tag{4.2}$$

- Extend above model (4.2) to logistic model for longitudinal binary data:

$$
\begin{aligned}
y_{ij}|b_i, x_i &\overset{ind}{\sim} \text{Binomial}\{1, \pi_{ij}^b(x_i)\}, \\
\text{logit}\{\pi_{ij}^b(x_i)\} &= \log\left\{\frac{\pi_{ij}^b(x_i)}{1-\pi_{ij}^b(x_i)}\right\} \\
&= \beta_0 + \beta_1 x_{ij1} + \cdots + \beta_p x_{ijp} + b_i \\
b_i &\sim \text{N}(0, \sigma_b^2),
\end{aligned}
\tag{4.3}
$$

  where b_i are the (normal) subject-specific random effects. This is a special GLMM (logistic-normal).

- **Remarks**:

  1. In this model the correlation is modeled through random effects b_i. A subject with higher b_i will have higher disease probability π_{ij}^b (if other covariate values are kept the same).

  2. Random effects b_i vary from subject to subject and are assumed to be independent. Hence the data $\{y_{ij}\}$ from the same

individuals are correlated.

3. The random effects b_i are usually assumed to have a normal distribution $N(0, \theta)$. The variance θ measures the between-subject variation, and also measures the strength of the correlation. If $\theta = 0$, no correlation. When θ increases, the correlation increases.

4. The success probability π_{ij}^b is subject-specific, so the parameters β's in (4.3) have a subject-specific interpretation (more detail in the infectious disease example).

5. For given x, $\pi(x)$ (the success probability for the population with covariate x) can be obtained through

$$\pi(x) = \mathrm{E}[\pi^b(x)] = \int \pi^b(x) f(b) db.$$

6. Even though $\pi^b(x)$ has a logistic form in model (4.3), $\pi(x)$ does **NOT** have a logistic form. In particular:

$$\text{logit}\{\pi(x)\} \neq \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p.$$

7. However, approximately we have

$$\text{logit}\{\pi(x)\} \approx (1+0.346\theta)^{-1/2} \times (\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p). \quad (4.4)$$

That is, $(1 + 0.346\theta)^{-1/2}\beta_k$ has a population-level interpretation in terms of log odds-ratio.

- Extend above model (4.2) to log-linear model for longitudinal Poisson (count) data:

$$
\begin{aligned}
y_{ij}|b_i &\overset{ind}{\sim} \text{Poisson}(\mu_{ij}^b = T_{ij}\lambda_{ij}^b), \\
\log(\lambda_{ij}^b) &= \beta_0 + \beta_1 x_{ij1} + \cdots + \beta_p x_{ijp} + b_i \\
\log(\mu_{ij}^b) &= \log(T_{ij}) + \beta_0 + \beta_1 x_{ij1} + \cdots + \beta_p x_{ijp} + b_i \\
b_i &\sim \text{N}(0, \sigma_b^2),
\end{aligned}
\tag{4.5}
$$

  where b_i are the (normal) subject-specific random effects. This is a special GLMM (Poisson-normal).

- **Remarks**:

  1. In this model, the correlation is modeled through random effects b_i. A subject with higher b_i will have larger rate λ_{ij}^b (if other covariate values are kept the same), and tend to have larger responses.

  2. Random effects b_i vary from subject to subject and are assumed to be independent. Hence the data $\{y_{ij}\}$ from the same

individuals are correlated.

3. The random effects b_i are usually assumed to have a normal distribution $N(0, \theta)$. The variance θ measures the between-subject variation, and also measures the strength of the correlation. If $\theta = 0$, no correlation. When θ increases, the correlation increases.

4. The event rate λ_{ij}^b is subject-specific, so the parameters β's in (4.5) have a subject-specific interpretation (more detail in the Epileptic seizure count example).

5. There still may be overdispersion for $y_{ij}|b_i$. That is $\mathrm{var}(y_{ij}|b_i) > \mathrm{E}(y_{ij}|b_i)$. So we may take the over-dispersion into account by assuming

$$\mathrm{var}(y_{ij}|b_i) = \phi \mathrm{E}(y_{ij}|b_i).$$

Note: This ϕ is different from the ϕ in GEE.

⋆ One way to account for overdispersion is to use statement `random _residual_` in Glimmix.

⋆ The other way is to assume $y_{ij}|b_i$ has the following log quasi-likelihood function:

$$\ell_q(y_{ij}, \mu_{ij}^b) = \frac{y_{ij}(\log \mu_{ij}^b - \log y_{ij}) - (\mu_{ij}^b - y_{ij})}{\phi} - \frac{1}{2}\log\phi.$$

⋆ Or to assume $y_{ij}|b_i$ has a generalized Poisson distribution:

$$f(y_{ij}|b_i) = \frac{(1-\xi)\mu_{ij}^b\{(1-\xi)\mu_{ij}^b + \xi y_{ij}\}^{y_{ij}-1}e^{-(1-\xi)\mu_{ij}^b - \xi y_{ij}}}{y_{ij}!}.$$

In this case,

$$\mathrm{E}(y_{ij}|b_i) = \mu_{ij}^b, \mathrm{var}(y_{ij}|b_i) = \mu_{ij}^b/(1-\xi)^2.$$

6. For given x, the population event rate $\lambda(x)$ (the event rate for the population with covariate x) can be obtained through

$$
\begin{aligned}
\lambda(x) &= \mathrm{E}[\lambda^b(x)] \\
&= \mathrm{E}\left[e^{\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p + b}\right] \\
&= e^{\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p} \mathrm{E}(e^b) \\
&= e^{\beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p} e^{\theta/2} \\
&= e^{\theta/2 + \beta_0 + \beta_1 x_1 + \cdots + \beta_p x_p} \\
&= e^{\tilde{\beta}_0 + \beta_1 x_1 + \cdots + \beta_p x_p}
\end{aligned}
$$

$$\Longrightarrow$$

$$\log\{\lambda(x)\} = \tilde{\beta}_0 + \beta_1 x_1 + \cdots + \beta_p x_p, \qquad (4.6)$$

therefore, the regression coefficients β's (except β_0) in model (4.5) also have population average interpretation.

- For a liner mixed model like the following

$$y_{ij} = \beta^T x_{ij} + b_{i0} + \epsilon_{ij},$$

where $\epsilon_{ij} \overset{iid}{\sim} \mathrm{N}(0, \sigma_\epsilon^2)$, we have

$$\mathrm{E}(y_{ij}|b_i) = \beta^T x_{ij} + b_{i0} \quad \text{and} \quad \mathrm{E}(y_{ij}) = \beta^T x_{ij}.$$

So the β's (except the intercept β_0) always have population-average interpretation as well as subject-specific interpretation.

- **Why GLMMs?**

  1. We are interested in how the outcome variable is related to the independent variables (covariates).

  2. We are also interested in how individuals' data vary from subject to subject (between-subject variation). This can be modeled through the use of random effects. The random effects have a natural interpretation.

  3. A GLMM is a likelihood-based model. So it requires much less strong assumption for missing data mechanism. Only MAR mechanism is required for a GLMM to make valid inference, compared to MCAR for GEE approach.

  4. The regression coefficients have a *subject-specific* interpretation, and for some special GLMMs we can still (approximately) make population level inference.

- **Implementation**: `Proc Glimmix` for GLMMs in `SAS` where approximate integration is used for approximate maximum quasi-likelihood estimation. Or `Proc Nlmixed` (non-linear mixed model) in `SAS` where numerical integration is used for maximum likelihood estimation.

4.3   Analyze infectious disease data using a GLMM

- Assume infection indicator y_{ij} (1 = infection, 0 = no infection):

$$y_{ij}|b_i \overset{ind}{\sim} \text{Binomial}(1, \pi_{ij}^b),$$

$$\text{logit}(\pi_{ij}^b) = \beta_0 + \beta_1 \text{Xero}_{ij} + \beta_2 \text{sinv}_{ij} + \beta_3 \text{age}_i$$

$$+ \beta_4 \text{time}_{ij} + \beta_5 \text{sex}_i + \beta_6 \text{height}_{ij} + b_i,$$

where $b_i \sim N(0, \theta)$.

- **Interpretation** of β_1 (coefficient of a time-varying covariate Xero): Let π_1^b, π_0^b be the infection probability for any subject i (the same kid) when Xero is 1 and 0 (while other covariate values are fixed). Then

$$\text{logit}(\pi_1^b) - \text{logit}(\pi_0^b) = \beta_1,$$

that is

$$\beta_1 = \log \left[\frac{\pi_1^b/(1-\pi_1^b)}{\pi_0^b/(1-\pi_0^b)} \right].$$

That is, β_1 is the log odds-ratio of getting respiratory infection if a subject becomes Vitamin A deficiency (from Vitamin A sufficiency). Similar interpretation holds for continuous time-varying covariates.

- **Interpretation** of β_5 (coefficient of a one-time covariate sex): Let $\pi_1^{b_i}$ be the infection probability for subject i who is a boy and $\pi_0^{b_j}$ be the infection probability for subject j who is a girl. Assume they have the same covariate values (except sex). Then

$$\mathrm{logit}(\pi_1^{b_i}) - \mathrm{logit}(\pi_0^{b_j}) = \beta_5 + (b_i - b_j).$$

If $b_i \approx b_j$, then

$$\text{logit}(\pi_1^{b_i}) - \text{logit}(\pi_0^{b_j}) \approx \beta_5,$$

$$\beta_5 \approx \log\left[\frac{\pi_1^{b_i}/(1 - \pi_1^{b_i})}{\pi_0^{b_j}/(1 - \pi_0^{b_j})}\right].$$

That is, β_5 is the log odds-ratio of getting respiratory infection comparing a boy and a girl who are similar in other subject characteristics except gender. Similar interpretation holds for continuous one-time covariates.

See the SAS program `indon_mix.sas` and its output `indon_mix.lst` for details.

- **Remark 1**: As indicated by (4.4), $(1 + 0.346\theta)^{-1/2}\beta$ have population log odds-ratio interpretation:

$$
\begin{aligned}
\text{logit}(\pi_{ij}) &\approx (1 + 0.346\theta)^{-1/2}\beta^T x_{ij} \\
&= \tilde{\beta}^T x_{ij},
\end{aligned}
$$

where $\tilde{\beta} = (1 + 0.346\theta)^{-1/2}\beta$. Therefore, $\tilde{\beta}$ has population-average interpretation. That is, we can use $\tilde{\beta}$ to compare two populations.

SAS program `indon_mix.sas`

```
options ls=80 ps=1000 nodate;

/*---------------------------------------------------*/
/*                                                   */
/* Proc Glimmix to fit subject-specific (random effect) */
/* model  for the Indonesian children infection disease */
/* data                                              */
/*                                                   */
/*---------------------------------------------------*/

data indon;
  infile "indon.dat";
  input id infect intercep age xero cosv sinv sex height stunted
  visit baseage season visitsq;
  time = age - baseage;
run;

title "Random intercept model for infection disease data";
proc glimmix data=indon method=quad;
  class id;
  model infect = xero sinv age time sex height / dist=bin link=logit s;
  random int / subject=id type=vc;
run;
```

SAS output `indon_mix.lst`

Random intercept model for infection disease data   1

The GLIMMIX Procedure

Model Information

```
Data Set                      WORK.INDON
Response Variable             infect
Response Distribution         Binomial
Link Function                 Logit
Variance Function             Default
Variance Matrix Blocked By    id
Estimation Technique          Maximum Likelihood
Likelihood Approximation      Gauss-Hermite Quadrature
Degrees of Freedom Method     Containment
```

Class Level Information

```
Class     Levels     Values

id           275     121013 121113 121114 121140 121215 121315
                     121316 ...
```

```
Number of Observations Read        1200
Number of Observations Used        1200
```

```
                          Dimensions

          G-side Cov. Parameters              1
          Columns in X                        7
          Columns in Z per Subject            1
          Subjects (Blocks in V)            275
          Max Obs per Subject                 6


                    Optimization Information

     Optimization Technique         Dual Quasi-Newton
     Parameters in Optimization     8
     Lower Boundaries               1
     Upper Boundaries               0
     Fixed Effects                  Not Profiled
     Starting From                  GLM estimates
     Quadrature Points              9
```

Iteration History

Iteration	Restarts	Evaluations	Objective Function	Change	Max Gradient
0	0	4	711.86096381	.	370.9219
1	0	4	706.20769988	5.65326394	299.1176
2	0	4	703.19922822	3.00847166	39.35369
3	0	3	702.16517109	1.03405713	35.20026
4	0	4	687.59198873	14.57318236	16.85617
5	0	4	685.75840614	1.83358259	6.4086
6	0	4	681.30002966	4.45837648	42.48172
7	0	3	680.48333006	0.81669960	24.84155
8	0	2	679.3625642	1.12076585	25.03619
9	0	3	678.98158225	0.38098196	9.369015
10	0	3	678.94174122	0.03984103	7.16441
11	0	3	678.92777026	0.01397095	9.372961
12	0	2	678.90767698	0.02009328	3.875721
13	0	3	678.9028667	0.00481028	0.136479
14	0	3	678.90284743	0.00001927	0.034321
15	0	3	678.90284698	0.00000045	0.009377

Convergence criterion (GCONV=1E-8) satisfied.

Fit Statistics

```
-2 Log Likelihood                   678.90
AIC  (smaller is better)            694.90
AICC (smaller is better)            695.02
BIC  (smaller is better)            723.84
CAIC (smaller is better)            731.84
HQIC (smaller is better)            706.51
```

Fit Statistics

```
-2 Log Likelihood              678.90
AIC  (smaller is better)       694.90
AICC (smaller is better)       695.02
BIC  (smaller is better)       723.84
CAIC (smaller is better)       731.84
HQIC (smaller is better)       706.51
```

Fit Statistics for Conditional Distribution

```
-2 log L(infect | r. effects)     579.67
Pearson Chi-Square                880.12
Pearson Chi-Square / DF             0.73
```

Covariance Parameter Estimates

Cov Parm	Subject	Estimate	Standard Error
Intercept	id	0.7141	0.3650

Solutions for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|
Intercept	-2.7427	0.2667	273	-10.29	<.0001
xero	0.5042	0.4860	920	1.04	0.2998
sinv	-0.05165	0.1588	920	-0.33	0.7451
age	-0.03727	0.007755	920	-4.81	<.0001
time	0.03999	0.02173	920	1.84	0.0660
sex	-0.4368	0.2613	920	-1.67	0.0949
height	-0.05349	0.02335	920	-2.29	0.0222

- **Remark 1 (subject-specific interpretation):** Since $\widehat{\beta}_1 = 0.5042$, so if a child becomes Vitamin A deficiency from Vitamin A sufficiency, his/her odds-ratio of getting respiratory infection will be $e^{0.5042} = 1.66$, that is, about 66% increase in risk.

- **Remark 2 (approximate population-average interpretation):** $\widehat{\theta} = 0.7141$, so $(1 + 0.346\widehat{\theta})^{-1/2} = 0.9$. So the population-average effect of Vitamin A deficiency is $0.9 \times 0.5042 = 0.454$. That is, given other covariates, the population of children with Vitamin A deficiency will be 57% (odds-ratio $e^{0.454} = 1.57 \approx$ relative risk if respiratory infection can be viewed as a rare event) more likely to have respiratory infection than the population of children without Vitamin A deficiency.

The population-average effect of sex is $0.9 \times (-0.4368) = -0.39$ (odds-ratio $= 0.65$). So boys are less likely to have respiratory infection than girls. Other effects can be obtained similarly.

- **Remark 3**: When the response y_{ij} is binary, we don't have to worry about over-dispersion for the conditional distribution of $y_{ij}|b_i$.

4.4   Analyze epileptic count data using a GLMM

- Assume seizure counts

$$y_{ij}|b_i \sim \text{Overdispersed} - \text{Poisson}(\mu_{ij}^b),$$

where

$$\mu_{ij}^b = \text{E}(y_{ij}|b_i) = t_{ij}\lambda_{ij}^b,$$

λ_{ij}^b is the rate to have a seizure for subject i. Consider model

$$
\begin{aligned}
\log(\lambda_{ij}^b) &= \beta_0 + \beta_1 I(j>0) + \beta_2 \text{trt}_i I(j>0) + b_i \\
\log(\mu_{ij}^b) &= log(t_{ij}) + \beta_0 + \beta_1 I(j>0) + \beta_2 \text{trt}_i I(j>0) + b_i,
\end{aligned}
$$

where $b_i \sim N(0,\theta)$ is a random intercept describing the between-subject variation.

- Interpretation of β's:

Group	$\log(\lambda^b)$ for random subject i	
	Before randomization	After randomization
Control (trt=0)	$\beta_0 + b_i$	$\beta_0 + \beta_1 + b_i$
Treatment (trt=1)	$\beta_0 + b_i$	$\beta_0 + \beta_1 + \beta_2 + b_i$

β_1: difference in log of rate of seizure counts comparing after randomization and before randomization for a random subject in control group (**time effect**).

β_2: difference in log of rate of seizure counts for a treated subject compared to if he/she received a placebo (**treatment effect**).

- For more details of the result, see SAS program `seize_mix.sas` and its output `seize_mix.lst`

- **Remark**: Since here we used the Poisson GLMM with log link and a random intercept, so the regression coefficients (except the intercept) also have population-average interpretation.

SAS program `seize_mix.sas`

```
options ls=80 ps=1000 nodate;

/*-------------------------------------------------------*/
/*                                                       */
/* Proc Glimmix to fit random intercept model to the     */
/* epileptic seizure count data                          */
/*                                                       */
/*-------------------------------------------------------*/

data seizure;
  infile "seize.dat";
  input id seize visit trt age;
  nobs=_n_;
  interval = 2;
  if visit=0 then interval=8;
  logtime = log(interval);
  assign = (visit>0);
  agn_trt = assign*trt;
run;


title "Random intercept model for seizure data with conditional overdispersion";
proc glimmix data=seizure;
  class id;
  model seize = assign agn_trt / dist=poisson link=log offset=logtime s;
  random int / subject=id type=vc;
  random _residual_;  *for conditional overdispersion;
run;
```

SAS output `seize_mix.lst`

Random intercept model for seizure data with conditional overdispersion   1

The GLIMMIX Procedure

Model Information

Data Set	WORK.SEIZURE
Response Variable	seize
Response Distribution	Poisson
Link Function	Log
Variance Function	Default
Offset Variable	logtime
Variance Matrix Blocked By	id
Estimation Technique	Residual PL
Degrees of Freedom Method	Containment

Class Level Information

Class	Levels	Values
id	59	101 102 103 104 106 107 108 110 111 112 113 114 ...

Number of Observations Read	295
Number of Observations Used	295

Dimensions

```
G-side Cov. Parameters            1
R-side Cov. Parameters            1
Columns in X                      3
Columns in Z per Subject          1
Subjects (Blocks in V)           59
Max Obs per Subject               5
```

Optimization Information

```
Optimization Technique        Dual Quasi-Newton
Parameters in Optimization    1
Lower Boundaries              1
Upper Boundaries              0
Fixed Effects                 Profiled
Residual Variance             Profiled
Starting From                 Data
```

Iteration History

Iteration	Restarts	Subiterations	Objective Function	Change	Max Gradient
0	0	4	609.19264304	0.49414053	0.000205
1	0	5	671.59595217	0.14411653	3.061E-6
2	0	3	675.96769701	0.01612221	0.000016
3	0	2	675.86073055	0.00032842	1.901E-8
4	0	1	675.85749753	0.00000336	3.111E-8
5	0	0	675.85746125	0.00000000	5.906E-6

Convergence criterion (PCONV=1.11022E-8) satisfied.

Fit Statistics

```
-2 Res Log Pseudo-Likelihood        675.86
Generalized Chi-Square              822.08
Gener. Chi-Square / DF                2.82
```

Covariance Parameter Estimates

			Standard
Cov Parm	Subject	Estimate	Error
Intercept	id	0.5704	0.1169
Residual (VC)		2.8154	0.2591

Solutions for Fixed Effects

		Standard			
Effect	Estimate	Error	DF	t Value	Pr > |t|
Intercept	1.0655	0.1079	58	9.88	<.0001
assign	0.1122	0.07723	234	1.45	0.1477
agn_trt	-0.1063	0.1054	234	-1.01	0.3144

- **Remark**: There is considerable amount of over-dispersion for $y_{ij}|b_i$. It is estimated that

$$\text{var}(y_{ij}|b_i) = 2.82\text{E}(y_{ij}|b_i).$$

- There is considerable between-patient variance in log-seizure rate. That variation is estimated to be 0.57.

- The regression coefficient estimates (except the intercept) have population-average interpretation except the intercept, and they are almost the same as those from the GEE model.

  For example, $\widehat{\beta}_2 = -0.1063$ with SE $= 0.1054$. Then if a subject switches from control to treatment, the rate of having seizure will decrease by 10% (since $e^{-0.1063} = 0.9$). The same rate deduction can also be used to compare treatment and control groups (i.e., population interpretation).

- If we would like to fit the data using the conditional quasi-likelihood approach, we need to use `Proc Nlmixed`:

```
proc nlmixed qpoints=15;
  parms beta0=-1.4 beta1=0.12 beta2=-0.12 theta=0.1 phi=1;
  eta = beta0 + beta1*assign + beta2*agn_trt + b;
  mu = interval*exp(eta);
  if seize=0 then
    l = -(mu - seize)/phi - log(phi)/2;
  else
    l = (seize*(log(mu) - log(seize)) - (mu - seize))/phi - log(phi)/2;
  model seize ~ general(l);
  random b ~ normal(0, theta) subject=id;
run;
```

The relevent output is

```
                             Parameter Estimates

                          Standard
Parameter    Estimate        Error      DF     t Value     Pr > |t|      Alpha        Lower

beta0          1.0350       0.1100       58        9.41     <.0001        0.05        0.8148
beta1          0.1123      0.07898       58        1.42     0.1603        0.05      -0.04577
beta2         -0.1065       0.1077       58       -0.99     0.3269        0.05       -0.3222
theta          0.5835       0.1204       58        4.85     <.0001        0.05        0.3426
phi            2.9456       0.2684       58       10.98     <.0001        0.05        2.4084
```

Therefore, the between-patient variance is estimated to be 0.5835 and the conditional over-dispersion parameter estimated to be $\widehat{\phi} = 2.9$. The inference on the treatment effect β_2 is similar.

- If we would like to fit a generalized Poisson distribution for the conditional distribution, we can use the following `Proc Nlmixed` program

```
proc nlmixed; * qpoints=15;
  parms beta0=-1.4 beta1=0.12 beta2=-0.12 theta=0.1 xi=0.5;
  bound theta>0, xi>-1, xi<1;

  eta = beta0 + beta1*assign + beta2*agn_trt + b;
  mu = interval*exp(eta);
  mu1 = (1-xi)*mu;
  mu2 = mu1 + xi*seize;

  l = log(mu1) + (seize-1)*log(mu2) - mu2 - lgamma(seize+1);

  model seize ~ general(l);
  random b ~ normal(0, theta) subject=id;
run;
```

The relevant output is

```
                              Parameter Estimates

                         Standard
Parameter     Estimate      Error      DF    t Value    Pr > |t|      Alpha       Lower

beta0          1.0635      0.1061      58      10.02     <.0001        0.05       0.8510
beta1          0.1256      0.08190     58       1.53     0.1307        0.05      -0.03837
beta2         -0.1150      0.1110      58      -1.04     0.3043        0.05      -0.3372
theta          0.5175      0.1076      58       4.81     <.0001        0.05       0.3020
xi             0.4516      0.03048     58      14.81     <.0001        0.05       0.3906
```

The estimated between-patient variance is $\widehat{\theta} = 0.52$ and the conditional over-dispersion is $1/(1 - \widehat{\xi})^2 = 1/(1 - 0.4516)^2 = 3.3$. The inference on the treatment effect β_2 is again similar.

5 Summary: what we covered

1. Advantages of longitudinal studies over other classical studies.

2. Challenge in analyzing data from longitudinal studies: correlation, within-subject and between-subject variation.

3. Linear mixed models for analyzing continuous longitudinal data: random effects are explicitly used to model the between-subject variation.

4. Generalized estimating equations (GEEs) for analyzing discrete longitudinal data when the correlation is not of major interest. Population-average interpretation.

5. Generalized linear mixed model for analyzing discrete longitudinal data where random effects are used to model the correlation. Subject-specific interpretation.