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 ($X = 0$). $\beta_1 > 0 \Longrightarrow$ 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

	D	$\overline{D}$
E	n_{11}	n_{10}
$\overline{E}$	n_{01}	n_{00}
	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.

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

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. $\cdots$

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:

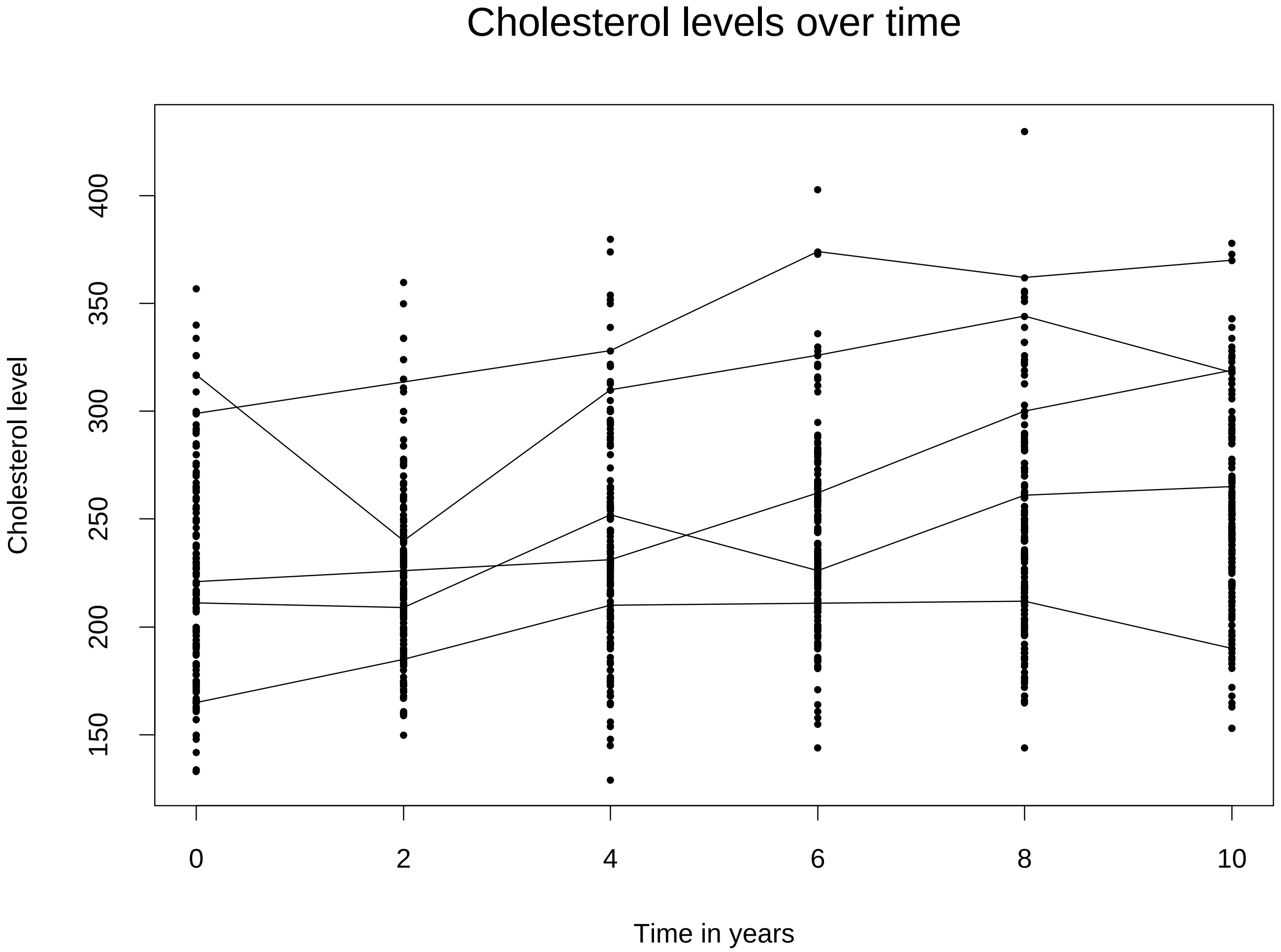
1. How does cholesterol level **change** over time on average as people get older?
2. How is the change of cholesterol level associated with sex and baseline age?
3. Do males have more stable (true) baseline cholesterol level and change rate than females?

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



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.

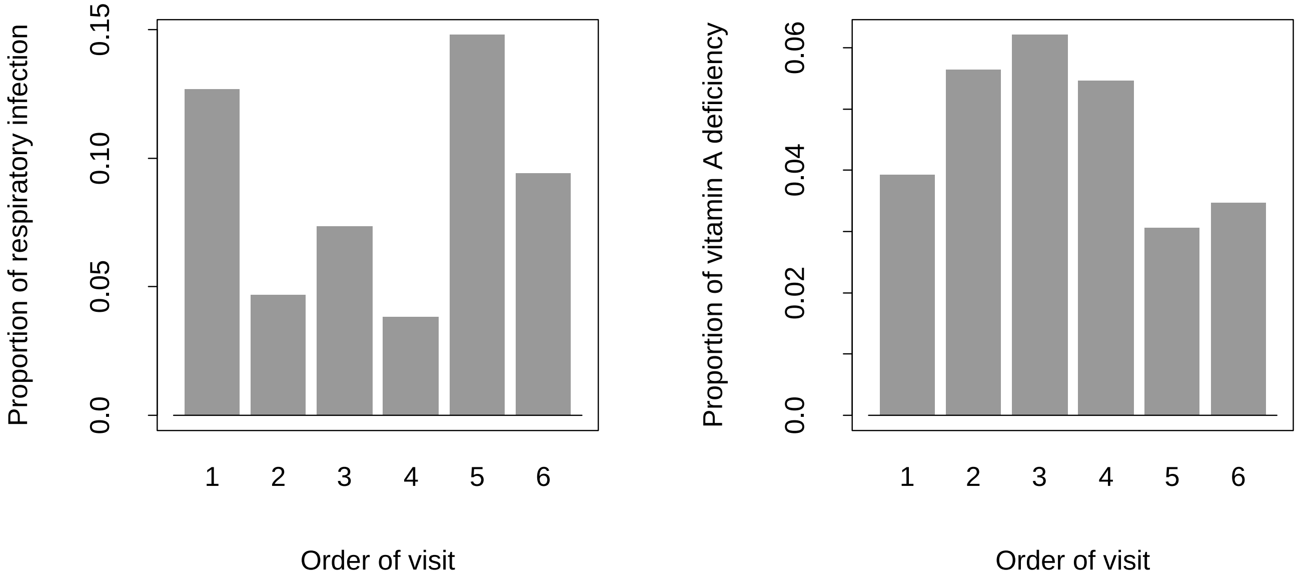
Study objectives:

- 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.

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.

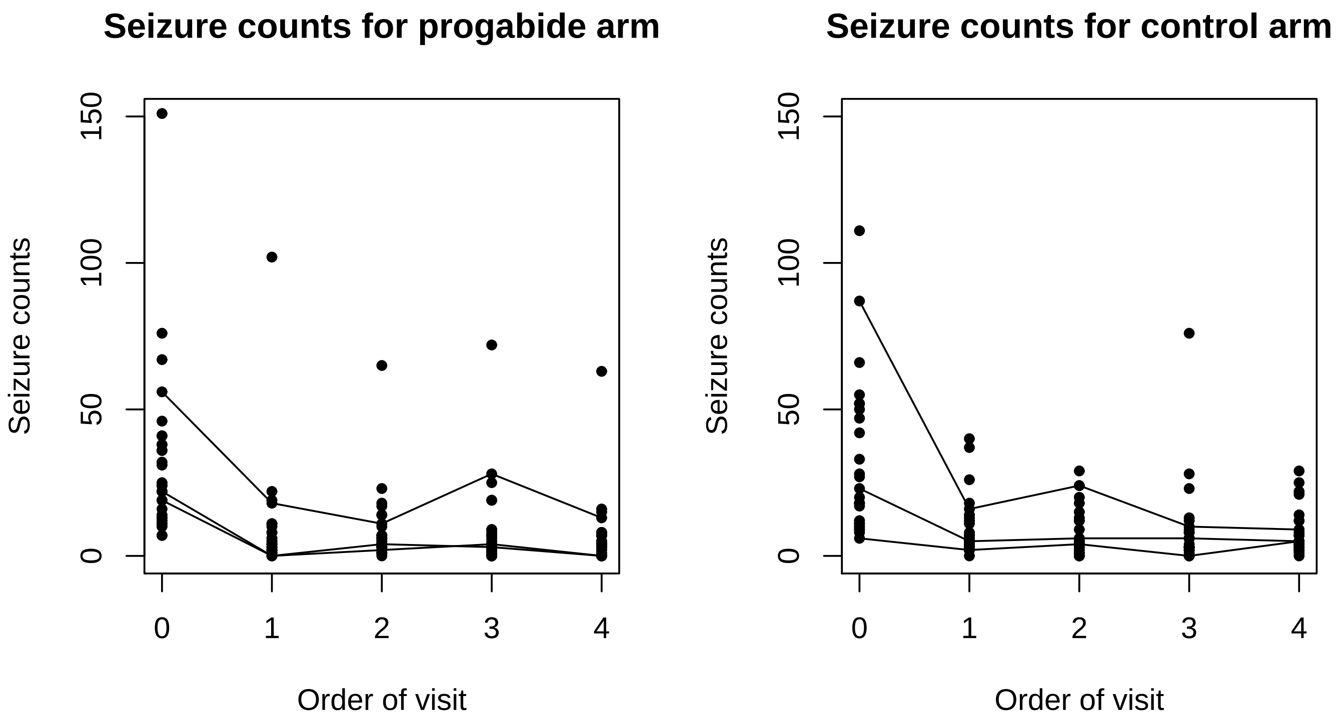
Study objectives:

- 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.

Epileptic seizure counts from the progabide trial



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

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

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

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

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

Then

$$y_{i1} = \beta_0 + \beta_C \text{age}_{i1} + \epsilon_{i1} \quad \text{(let } j = 1\text{)},$$
$$y_{ij} - y_{i1} = \beta_L(\text{age}_{ij} - \text{age}_{i1}) + \epsilon_{ij} - \epsilon_{i1}.$$

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 $Y = b + e$, where $e \sim (0, \sigma_e^2)$ is the measurement error.

   - $\sigma_e^2 =$ 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_e^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

$$Y_{ij} = b_i + e_{ij}.$$

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

$$y_i = \beta_0 + \beta_1 \mathrm{age}_i + \beta_2 \mathrm{sex}_i + \epsilon_i.$$

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:

$$y_{ij} = b_i + e_{ij},$$

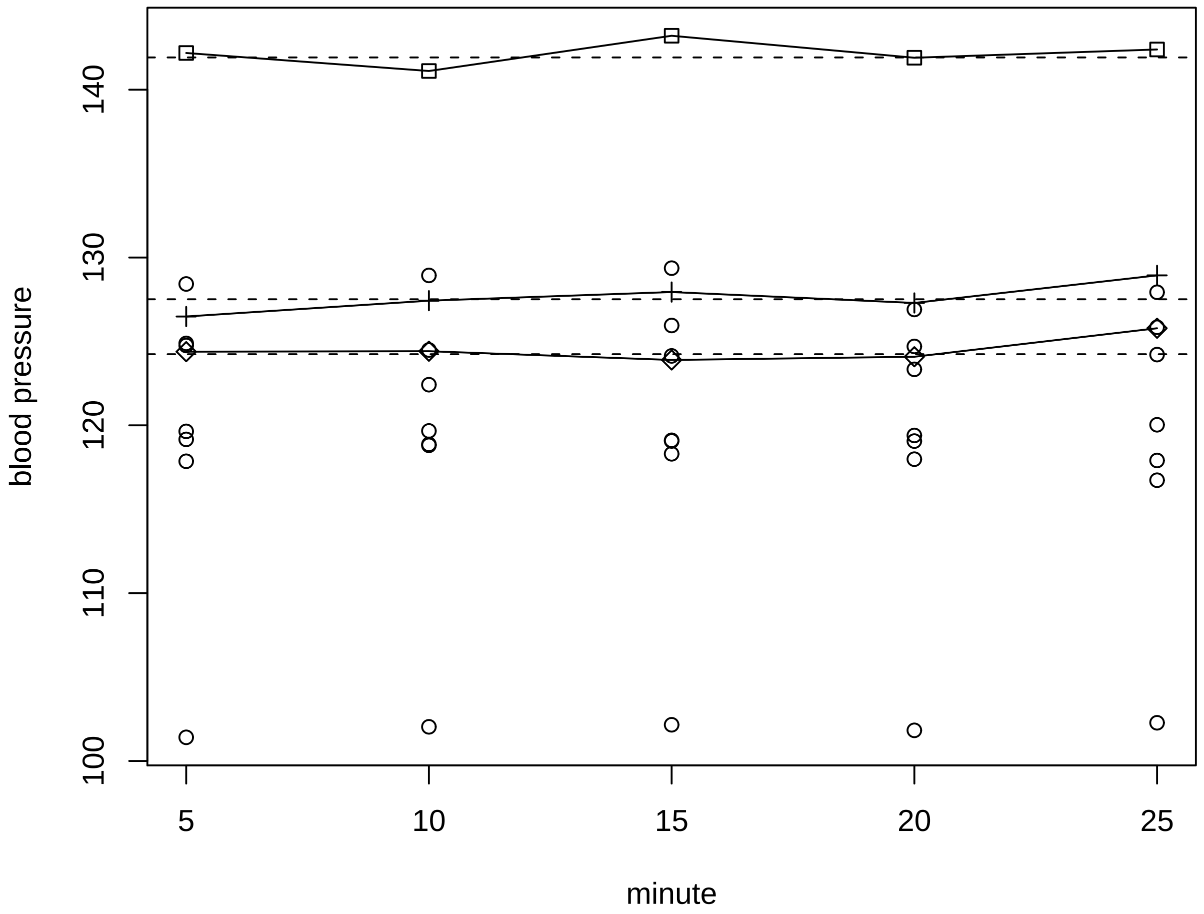
   where b_i is the true blood pressure of subject i, e_{ij} is the independent (random) measurement error, independent of b_i.

For $j \neq k$,

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

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:

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

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 mixed model approach can do the same even better.
2. Mixed (effects) model approach: model fixed effects and random effects; use random effect 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:

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

     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

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

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

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

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 statistics 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	$< .0001$	$\widehat{\text{corr}}(\widehat{b}_0, \widehat{b}_1) = -0.27$

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

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

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

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 var(b_0) and var(b_1) between males and females.
3. Try to examine the effects of age and sex on b_0 using

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

   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 age, sex";
proc reg data=main;
  model b0hat = sex age;
run;

title "Regression to look at the association between slope and age, sex";
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 age, sex     5

                              The REG Procedure
                                Model: MODEL1
                           Dependent Variable: b0hat

                             Analysis of Variance

                                    Sum of           Mean
Source                   DF        Squares         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

                          Parameter       Standard
     Variable     DF       Estimate          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 age, sex       6

                                    The REG Procedure
                                      Model: MODEL1
                                Dependent Variable: b1hat

                                   Analysis of Variance

                                            Sum of           Mean
       Source                   DF         Squares         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

                                  Parameter       Standard
            Variable     DF        Estimate          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:

$$\begin{aligned} \widehat{\mathrm{E}}(\widehat{b}_0) &: 223.97(\text{female}), 217.6(\text{male}), \text{p-value} = 0.28 \\ \widehat{\mathrm{E}}(\widehat{b}_1) &: 1.75(\text{female}), 3.31(\text{male}), \text{p-value} = 0.002. \end{aligned}$$

2. Comparison of var(b_0) and var(b_1) between males and females:

$$\begin{aligned} S^2_{\widehat{b}_0} &: 1621(\text{female}), 1848(\text{male}), \text{p-value} = 0.5 \\ S^2_{\widehat{b}_1} &: 11.3(\text{female}), 13.9(\text{male}), \text{p-value} = 0.3. \end{aligned}$$

   However, the above tests do NOT compare var(b_0) and 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:

$$\begin{aligned} \widehat{b}_0 &= \alpha_0 + \alpha_1 \text{sex} + \alpha_2 \text{age} + e_0, \\ & \quad \widehat{\alpha}_0 = 138.2(15.0), \quad \widehat{\alpha}_1 = -9.75(5.5), \quad \widehat{\alpha}_2 = 2.06(0.35). \end{aligned}$$

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:

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

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 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
$\cdots$			
i	$y_{i1}, y_{i2}, ..., y_{in_i}$	$t_{i1}, t_{i2}, ..., t_{in_i}$	b_i
$\cdots$			
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 $i \Longrightarrow b_i =$ 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: $\text{Var}(y_{ij}) = \sigma_b^2 + \sigma_\varepsilon^2$, 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

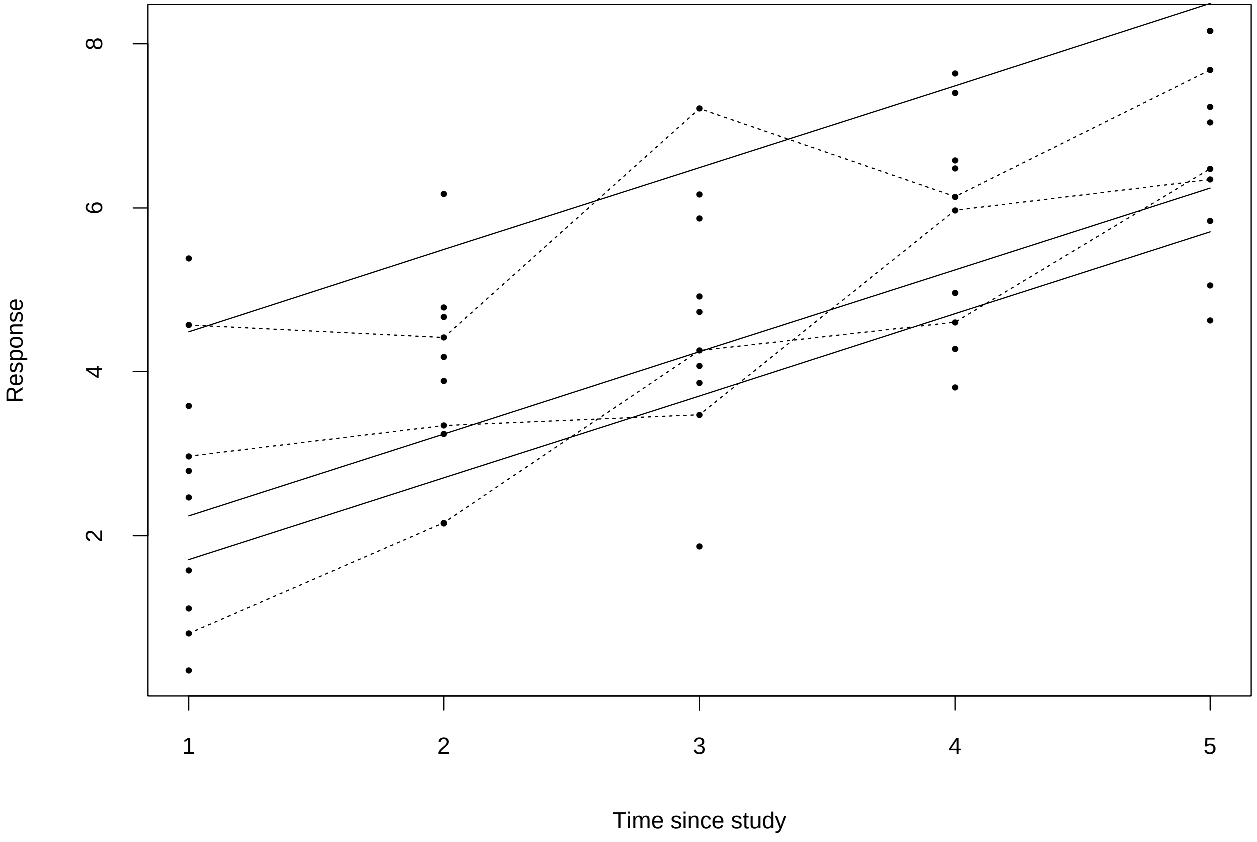
1. Treating b_i as random enables us to make inference for the whole population from which the sample was drawn. Treating b_i as fixed would only allow us to make inference for the study sample.

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}; $\varepsilon_{ij} \sim \mathrm{N}(0, \sigma_\varepsilon^2)$.

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 $i \Longrightarrow b_{i0} =$ deviation of intercept of subject i from population intercept β_0

5. $\beta_1 + b_{i1} =$ the slope for subject $i \Longrightarrow b_{i1} =$ 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. $\sigma_\varepsilon^2 =$ within-subject variance.

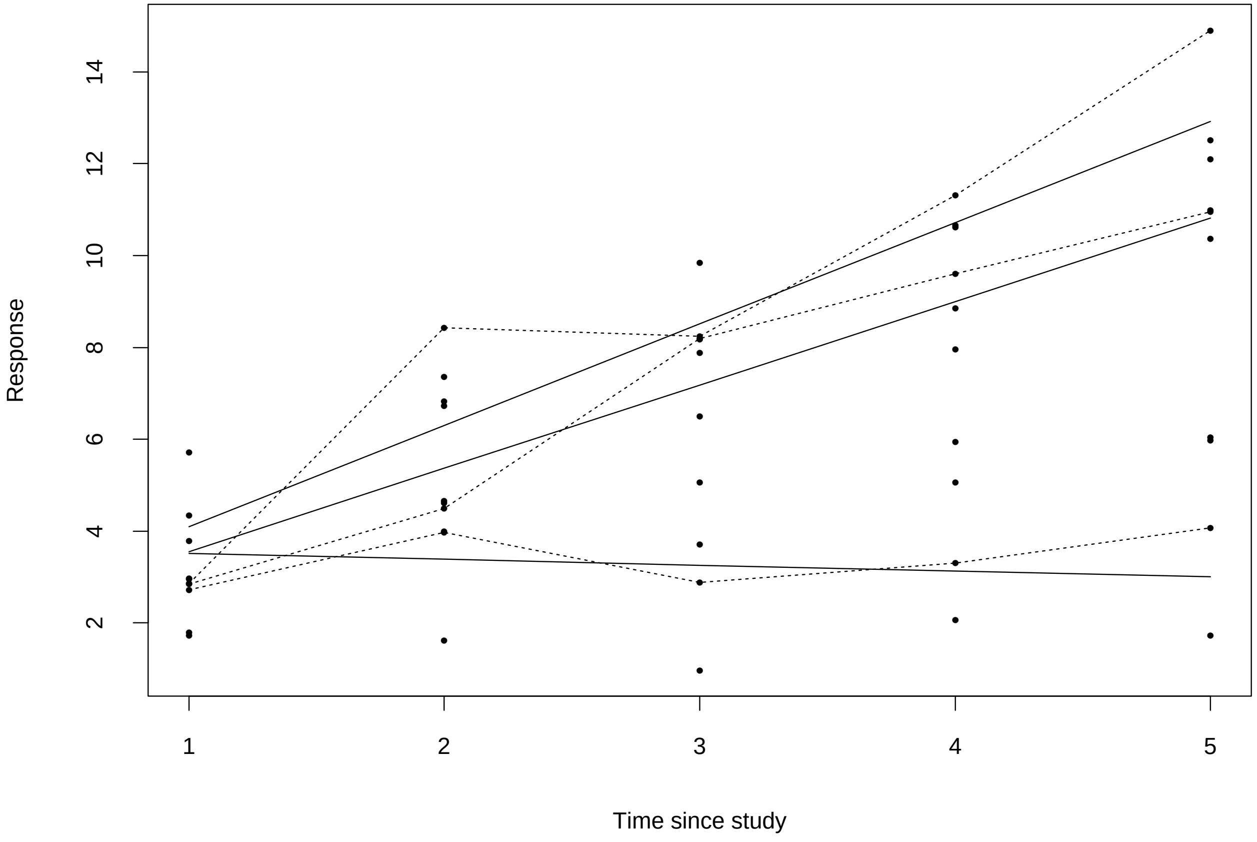
8. Total variance of y: Var$(y_{ij}) = \sigma_{00} + 2t_{ij}\sigma_{01} + t_{ij}^2\sigma_{11} + \sigma_\varepsilon^2$, not a constant over time.

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

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

where ϵ_{ij} are correlated normal errors (contains random effects and ε_{ij}).

For example,

1. Compound symmetric (exchangeable) variance matrix

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

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

2. AR(1) variance matrix

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

Here, $-1 < \rho < 1$. It assumes that the error $(\epsilon_{i1}, \epsilon_{i2}, \epsilon_{i3})$ 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

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

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

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

Here no restriction is imposed on σ_{ij}.

IV. General linear mixed models

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

For example,

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

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 */
                                           /* for random effects */
  repeated / subject=id type=vc; /* specify the variance structure for error */
run;
```

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 */
                                           /* 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 */
                                           /* 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=sp(pow)(t) local; /* cat_t is class t  */
```

2.2 Estimation and inference for linear mixed models

Let θ consist of all parameters in random effects and errors (ε_{ij}). We want to make inference on β and θ. There are two approaches:

1. Maximum likelihood:

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

   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 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

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

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

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

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

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

Therefore, β_0, β_1 are fixed effects and a_{i0}, a_{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. $\widehat{\text{corr}}(b_0, b_1) = \widehat{\text{corr}}(a_0, a_1) = -2.2259/\sqrt{1467 \times 3.84} = -0.03$, as compared to $\widehat{\text{corr}}(\widehat{b}_0, \widehat{b}_1) = -0.27$.
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. $\widehat{\sigma}^2_{\varepsilon} = 434.11$.

⋆ **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:

$$b_{i0} = \beta_0 + \beta_C age_i + a_{i0} \tag{2.3}$$

$$b_{i1} = \beta_1 + \beta_A age_i + a_{i1}, \tag{2.4}$$

    Where age_i is individual i's baseline age. 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 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 (a_{i0}, a_{i1}):

$$\left(\begin{array}{c} a_{i0} \\ a_{i1} \end{array}\right) \sim N\left(\left[\begin{array}{c} 0 \\ 0 \end{array}\right], \left[\begin{array}{cc} \sigma_{00} & \sigma_{01} \\ \sigma_{01} & \sigma_{11} \end{array}\right]\right).$$

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).

- ⋆ Basic model (2.1) becomes

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

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

⋆ 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

                                     Standard
   Effect            Estimate         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

                              Num     Den
            Effect             DF      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

                                   Standard
    Label           Estimate         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 $\text{H}_0 : \beta_L = \beta_C$ is 0.0473, significant at level 0.05!
7. $\widehat{\sigma}^2_\varepsilon = 434.15$ is basically the same as the corresponding estimate from model (2.1), which is 434.11.
8. Similarly, we can test iid ε_{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:

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

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

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

  ⋆ 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

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

- ⋆ 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 $\mathsf{H}_0 : \beta_{1,sex} - 10\beta_{1,age} = 0$.

⋆ 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

                         Standard
Effect       Estimate       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

                                Std Err
Effect      newid   Estimate       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

                           Standard
  Label        Estimate       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. $\widehat{\sigma}^2_{\varepsilon} = 434.15$, 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:

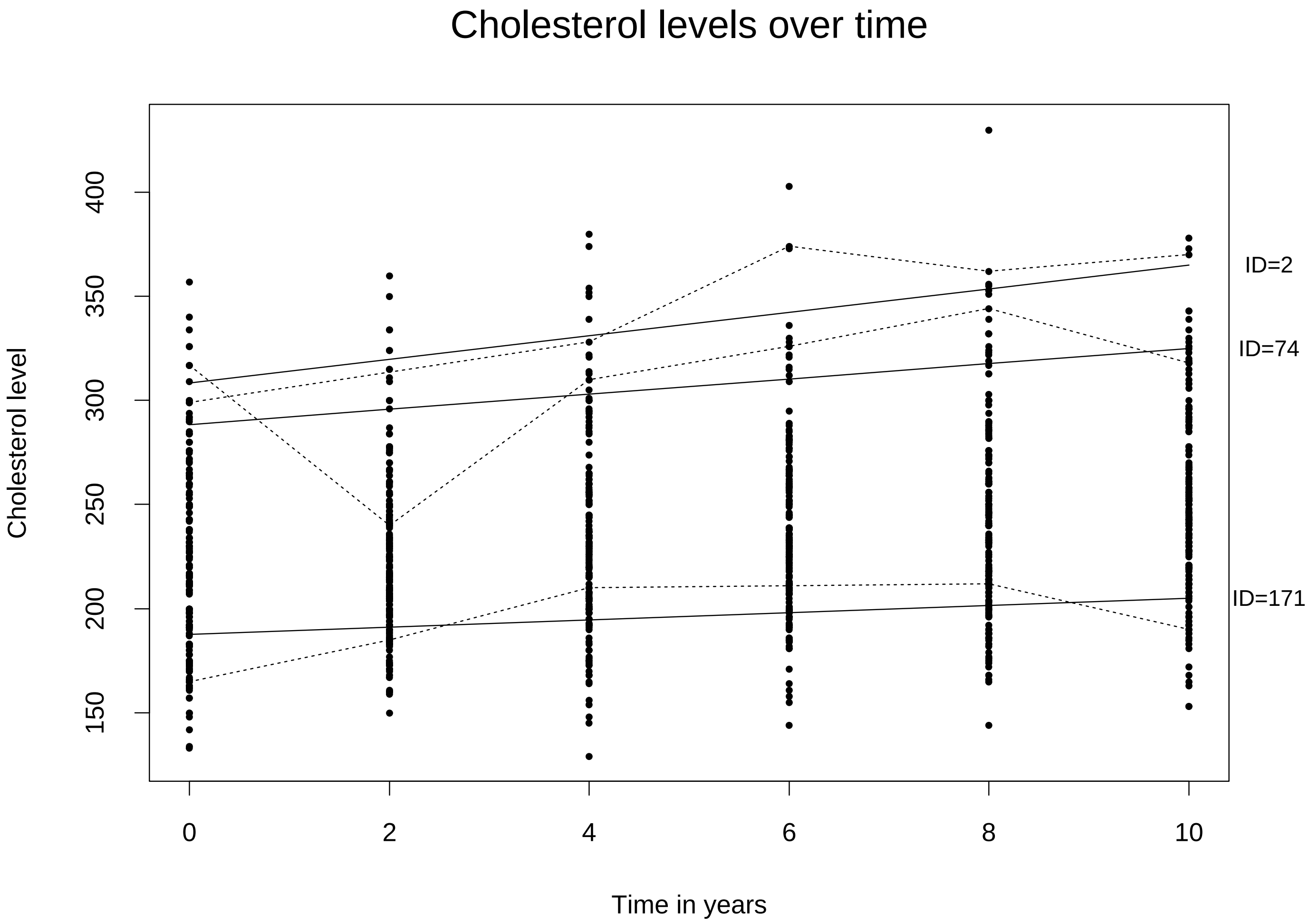
$$\begin{aligned}\text{Model (2.8) :}\quad & \widehat{\beta}_0 = 138.18(SE = 14.9),\\ & \widehat{\beta}_{0,sex} = -9.64(SE = 5.43),\ \widehat{\beta}_{0,age} = 2.05(SE = 0.35)\\ \text{Two-stage :}\quad & \widehat{\alpha}_0 = 138.2(SE = 15.0),\\ & \widehat{\alpha}_1 = -9.75(SE = 5.48),\ \widehat{\alpha}_2 = 2.06(SE = 0.35).\end{aligned}$$

(b) Effect on change rate of cholesterol level:

$$\begin{aligned}\text{Model (2.8) :}\quad & \widehat{\beta}_1 = 6.80(SE = 1.22),\\ & \widehat{\beta}_{1,sex} = 1.80(SE = 0.45), \widehat{\beta}_{1,age} = -0.11(SE = 0.03).\\ \text{Two-stage :}\quad & \widehat{\beta}_0 = 6.14(SE = 1.35),\\ & \widehat{\beta}_1 = 1.74(SE = 0.49),\ \widehat{\beta}_2 = -0.11(SE = 0.03).\end{aligned}$$

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

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



- 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:

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

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

  ⋆ We would like to test
  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:

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

  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

```
                   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.
```

```
                          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

                                 Standard
     Effect       Estimate          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

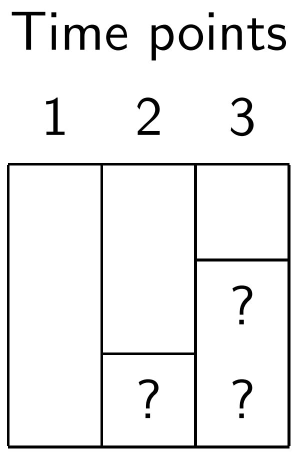
However, GEE will be less efficient if a correct model can be specified; with missing data, the missing data mechanism has to be *missing completely at random* (MCAR) for the GEE inference to be valid.

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



   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

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

	Δ							
ρ	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,

$$
\begin{aligned}
& y_{ij} \sim \text{Binomial}\{1, \pi_{ij}(x_{ij})\} \\
& \text{logit}\{\pi_{ij}(x_{ij})\} = \beta_0 + \beta_1 \text{season}_{ij} + \beta_2 \text{Xero}_{ij} + \beta_3 \text{age}_i \\
& + \beta_4 \text{time}_{ij} + \beta_5 \text{sex}_i + \beta_6 \text{height}_{ij},
\end{aligned}
$$

   $\pi_{ij}(x_{ij}) = P[y_{ij} = 1|x_{ij}] = \text{E}(y_{ij}|x_{ij})$ 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

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

where

$$\begin{aligned}
\Sigma &= I_0^{-1} I_1 I_0^{-1} \\
I_0 &= \sum_{i=1}^{m} D_i^T V_i^{-1} D_i \\
I_1 &= \sum_{i=1}^{m} D_i^T V_i^{-1} \mathrm{var}(y_i|x_i) V_i^{-1} D_i \\
&= \sum_{i=1}^{m} D_i^T V_i^{-1} (y_i - \mu_i(\widehat{\beta}))(y_i - \mu_i(\widehat{\beta}))^T V_i^{-1} D_i
\end{aligned}$$

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

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

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), $\Longrightarrow$

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

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(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 $\sim \mathrm{Bin}(1, \pi_{ij})$,

$$\begin{aligned} \mathrm{logit}(\pi_{ij}) &= \beta_0 + \beta_1 \mathrm{season}_{ij} + \beta_2 \mathrm{Xero}_{ij} + \beta_3 \mathrm{age}_i \\ &\quad + \beta_4 \mathrm{time}_{ij} + \beta_5 \mathrm{sex}_i + \beta_6 \mathrm{height}_{ij} \end{aligned}$$

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;
run;

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

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

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

SAS output: `indon_gee.lst`

```
                    Model 1: Use exchangeable working correlation                2

                                  The GENMOD Procedure

                                   Model Information

                          Data Set                 WORK.INDON
                          Distribution               Binomial
                          Link Function                 Logit
                          Dependent Variable           infect
                          Observations Used              1200


                                Class Level Information

          Class      Levels    Values

          id            275    121013 ...


                                    Response Profile

                           Ordered                    Total
                             Value    infect    Frequency

                                 1    1               107
                                 2    0              1093

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

```
                    Criteria For Assessing Goodness Of Fit

                Criterion                 DF           Value        Value/DF

                Deviance                1193        685.3920          0.5745
                Scaled Deviance         1193        694.9775          0.5825
                Pearson Chi-Square      1193       1176.5455          0.9862
                Scaled Pearson X2       1193       1193.0000          1.0000
                Log Likelihood                     -347.4888

        Algorithm converged.


                       Analysis Of Initial Parameter Estimates

                                  Standard      Wald 95%          Chi-
           Parameter  DF  Estimate    Error   Confidence Limits   Square  Pr > ChiSq

           Intercept   1   -2.3572   0.3435  -3.0305   -1.6838     47.08      <.0001
           season      1   -0.0424   0.1098  -0.2576    0.1728      0.15      0.6995
           xero        1    0.6657   0.4313  -0.1796    1.5110      2.38      0.1227
           baseage     1   -0.0333   0.0064  -0.0458   -0.0209     27.47      <.0001
           time        1    0.0006   0.0199  -0.0384    0.0397      0.00      0.9753
           sex         1   -0.3841   0.2173  -0.8099    0.0418      3.12      0.0771
           height      1   -0.0462   0.0205  -0.0864   -0.0061      5.09      0.0240
           Scale       0    0.9931   0.0000   0.9931    0.9931

        NOTE: The scale parameter was estimated by the square root of Pearson's
              Chi-Square/DOF.
```

```
                         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      0.0462      0.0462      0.0462      0.0462      0.0462
    Row2    0.0462      1.0000      0.0462      0.0462      0.0462      0.0462
    Row3    0.0462      0.0462      1.0000      0.0462      0.0462      0.0462
    Row4    0.0462      0.0462      0.0462      1.0000      0.0462      0.0462
    Row5    0.0462      0.0462      0.0462      0.0462      1.0000      0.0462
    Row6    0.0462      0.0462      0.0462      0.0462      0.0462      1.0000


                     Analysis Of GEE Parameter Estimates
                      Empirical Standard Error Estimates

                         Standard   95% Confidence
           Parameter Estimate    Error       Limits            Z Pr > |Z|

           Intercept  -2.3504   0.3332  -3.0036  -1.6973   -7.05   <.0001
           season     -0.0409   0.0889  -0.2151   0.1334   -0.46   0.6457
           xero        0.5525   0.4472  -0.3240   1.4291    1.24   0.2167
           baseage    -0.0338   0.0061  -0.0458  -0.0217   -5.49   <.0001
           time        0.0017   0.0216  -0.0407   0.0440    0.08   0.9385
           sex        -0.4021   0.2375  -0.8675   0.0633   -1.69   0.0903
           height     -0.0493   0.0258  -0.0999   0.0014   -1.91   0.0566
```

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 $e^{0.5525} = 1.74$. 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=0.2167 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 the 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;
run;
```

Output of the above program:

```
                    Model 1: overall effect of the treatment                   1

                              The GENMOD Procedure

                               Model Information

                      Data Set                  WORK.SEIZURE
                      Distribution                   Poisson
                      Link Function                      Log
                      Dependent Variable               seize
                      Offset Variable                logtime
                      Observations Used                  295


                            Class Level Information

        Class      Levels    Values

        id             59    101 102 ...


                     Criteria For Assessing Goodness Of Fit

            Criterion                 DF           Value        Value/DF

            Deviance                 291       3577.8316         12.2950
            Scaled Deviance          291       3577.8316         12.2950
            Pearson Chi-Square       291       5733.4815         19.7027
            Scaled Pearson X2        291       5733.4815         19.7027
            Log Likelihood                     6665.9803

        Algorithm converged.
```

```
                       Analysis Of Initial Parameter Estimates

                              Standard       Wald 95%         Chi-
   Parameter   DF  Estimate      Error   Confidence Limits   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
   Scale        0    1.0000     0.0000    1.0000    1.0000

 NOTE: The scale parameter was held fixed.


                               GEE Model Information

                    Correction 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.

                         Analysis Of GEE Parameter Estimates
                         Empirical Standard Error Estimates

                              Standard   95% Confidence
         Parameter  Estimate     Error       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;
run;
```

Output from the above program:

```
                Model 2: take randomization into account                     2

                           The GENMOD Procedure

                            Model Information

                    Data Set                    WORK.SEIZURE
                    Distribution                     Poisson
                    Link Function                        Log
                    Dependent Variable                 seize
                    Offset Variable                  logtime
                    Observations Used                    295


                          Class Level Information

    Class       Levels    Values

    id              59    101 102  ...
```

```
                    Criteria For Assessing Goodness Of Fit

        Criterion                 DF           Value        Value/DF

        Deviance                 292       3578.1542         12.2540
        Scaled Deviance          292        182.1888          0.6239
        Pearson Chi-Square       292       5734.8269         19.6398
        Scaled Pearson X2        292        292.0000          1.0000
        Log Likelihood                      339.4033


Algorithm converged.


                   Analysis Of Initial Parameter Estimates

                              Standard      Wald 95%          Chi-
Parameter    DF  Estimate       Error   Confidence Limits   Square  Pr > ChiSq

Intercept     1    1.3616      0.1033    1.1592    1.5640   173.89      <.0001
assign        1    0.0968      0.1762   -0.2486    0.4422     0.30      0.5829
assign*trt    1   -0.0772      0.2007   -0.4706    0.3163     0.15      0.7007
Scale         0    4.4317      0.0000    4.4317    4.4317

NOTE: The scale parameter was estimated by the square root of Pearson's
      Chi-Square/DOF.
```

```
                         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.

                  Analysis Of GEE Parameter Estimates
                  Empirical Standard Error Estimates

                        Standard   95% Confidence
      Parameter  Estimate    Error       Limits            Z Pr > |Z|

      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;
run;
```

Output of the program to adjust for all covariates

```
                 Model 3: adjusting for other covariates                    3

                           The GENMOD Procedure

                            Model Information

                    Data Set                     WORK.SEIZURE
                    Distribution                      Poisson
                    Link Function                         Log
                    Dependent Variable                  seize
                    Offset Variable                   logtime
                    Observations Used                     295


                         Class Level Information

       Class      Levels    Values

       id             59    101 ...
```

```
                  Criteria For Assessing Goodness Of Fit

         Criterion                 DF           Value        Value/DF

         Deviance                 290       3523.4645         12.1499
         Scaled Deviance          290        186.4540          0.6429
         Pearson Chi-Square       290       5480.1978         18.8972
         Scaled Pearson X2        290        290.0000          1.0000
         Log Likelihood                      354.1875


     Algorithm converged.


                     Analysis Of Initial Parameter Estimates

                                   Standard      Wald 95%          Chi-
     Parameter   DF  Estimate      Error   Confidence Limits   Square  Pr > ChiSq

     Intercept    1    1.9085     0.3614    1.2002    2.6168    27.89      <.0001
     assign       1    0.1108     0.2038   -0.2887    0.5103     0.30      0.5867
     trt          1    0.0005     0.2036   -0.3986    0.3996     0.00      0.9981
     assign*trt   1   -0.1037     0.2828   -0.6580    0.4506     0.13      0.7139
     age          1   -0.0196     0.0116   -0.0424    0.0032     2.83      0.0926
     Scale        0    4.3471     0.0000    4.3471    4.3471

    NOTE: The scale parameter was estimated by the square root of Pearson's
          Chi-Square/DOF.
```

```
                           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.


                      Analysis Of GEE Parameter Estimates
                      Empirical Standard Error Estimates

                            Standard   95% Confidence
            Parameter  Estimate    Error       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 ⇒ discrete**)
  2. logistic (Poisson) models (**independent discrete data ⇒ 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 $b_i \sim \mathrm{N}(0, \sigma_b^2)$ and $\varepsilon_{ij} \overset{iid}{\sim} \mathrm{N}(0, \sigma_\varepsilon^2)$.
Let $\mu_{ij}^b = \mathrm{E}[y_{ij}|b_i]$. Then the above model is equivalent to

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

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

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

  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:

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

  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

$$
\begin{aligned}
\lambda(x) &= \mathrm{E}[\lambda^b(x)] \\
&= \mathrm{E}\left[e^{\beta_0+\beta_1 x_1+\cdots+\beta_p x_p+b}\right] \\
&= e^{\beta_0+\beta_1 x_1+\cdots+\beta_p x_p}\mathrm{E}(e^b) \\
&= e^{\beta_0+\beta_1 x_1+\cdots+\beta_p x_p}e^{\theta/2} \\
&= e^{\theta/2+\beta_0+\beta_1 x_1+\cdots+\beta_p x_p} \\
&= e^{\tilde{\beta}_0+\beta_1 x_1+\cdots+\beta_p x_p} \\
&\Longrightarrow \\
\log\{\lambda(x)\} &= \tilde{\beta}_0+\beta_1 x_1+\cdots+\beta_p x_p, \qquad (4.6)
\end{aligned}
$$

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):

$$\begin{aligned} y_{ij}|b_i &\overset{ind}{\sim} \text{Binomial}(1, \pi_{ij}^b), \\ \text{logit}(\pi_{ij}^b) &= \beta_0 + \beta_1 \text{season}_{ij} + \beta_2 \text{Xero}_{ij} + \beta_3 \text{age}_i \\ &\quad + \beta_4 \text{time}_{ij} + \beta_5 \text{sex}_i + \beta_6 \text{height}_{ij} + b_i, \end{aligned}$$

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

- **Interpretation** of β_2 (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

$$\text{logit}(\pi_1^b) - \text{logit}(\pi_0^b) = \beta_2,$$

that is

$$\beta_2 = \log\left[\frac{\pi_1^b/(1-\pi_1^b)}{\pi_0^b/(1-\pi_0^b)}\right].$$

That is, β_2 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

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

If $b_i \approx b_j$, then

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

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:

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

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 = season xero 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

                                              Objective                      Max
  Iteration    Restarts    Evaluations         Function          Change    Gradient

          0           0              4     711.85214926           .         370.248
          1           0              4     705.17377387      6.67837539    325.4556
          2           0              4     701.66091706      3.51285681    63.11033
          3           0              2     698.22850425      3.43241282    133.8429
          4           0              2     694.02433064      4.20417361    29.58844
          5           0              4     688.64294661      5.38138403    44.45273
          6           0              2      684.7338452      3.90910141    36.74223
          7           0              3     682.76342298      1.97042222    5.605872
          8           0              2     680.11119418      2.65222880    49.52205
          9           0              3     679.63453452      0.47665966    37.21899
         10           0              2     679.03086357      0.60367095    34.80307
         11           0              3      678.8643414      0.16652217    7.530059
         12           0              3     678.86037714      0.00396426    2.913637
         13           0              3     678.85888563      0.00149150    2.037862
         14           0              2     678.85638762      0.00249801    1.749602
         15           0              3      678.8553423      0.00104532    0.476605
         16           0              3     678.85532391      0.00001839    0.072154
         17           0              3      678.8553228      0.00000111    0.005773

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


                              Fit Statistics

                       -2 Log Likelihood            678.86
                       AIC  (smaller is better)     694.86
                       AICC (smaller is better)     694.98
                       BIC  (smaller is better)     723.79
                       CAIC (smaller is better)     731.79
                       HQIC (smaller is better)     706.47
                   Fit Statistics for Conditional
                           Distribution

              -2 log L(infect | r. effects)      579.13
              Pearson Chi-Square                 880.70
              Pearson Chi-Square / DF              0.73


                   Covariance Parameter Estimates

                                                    Standard
             Cov Parm     Subject    Estimate          Error

             Intercept    id           0.7187         0.3656


                    Solutions for Fixed Effects

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

  Intercept     -2.6258           0.3892       273      -6.75      <.0001
  season       -0.04536           0.1158       920      -0.39      0.6954
  xero           0.5015           0.4862       920       1.03      0.3026
  age          -0.03715         0.007748       920      -4.79      <.0001
  time          0.04046          0.02175       920       1.86      0.0632
  sex           -0.4374           0.2615       920      -1.67      0.0947
  height       -0.05212          0.02327       920      -2.24      0.0254
```

- **Remark 1 (subject-specific interpretation):** Since $\widehat{\beta}_2 = 0.5015$, so if a child becomes Vitamin A deficiency from Vitamin A sufficiency, his/her odds-ratio of getting respiratory infection will be $e^{0.5015} = 1.65$, that is, about 65% increase in risk.

- **Remark 2 (approximate population-average interpretation):** $\widehat{\theta} = 0.7187$, so $(0.346 \times \widehat{\theta} + 1)^{-1/2} = 0.89$. So the population-average effect of Vitamin A deficiency is $0.89 \times 0.5015 = 0.446$. That is, given other covariates, the population of children with Vitamin A deficiency will be 56% (odds-ratio $e^{0.446} = 1.56 \approx$ 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 $0.89 \times (-0.4374) = -0.39$ (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

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

where

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

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

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

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

                                          Objective                        Max
 Iteration   Restarts   Subiterations      Function          Change   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.