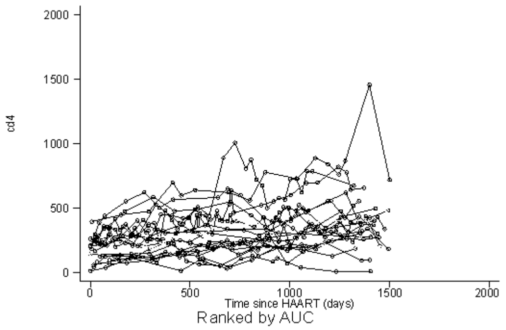
Longitudinal Data
Spring 2013
March 6



Chapter 5

Introduction to Approaches to Repeated Measures

Chapter 6

Estimation of Marginal (GEE) Models

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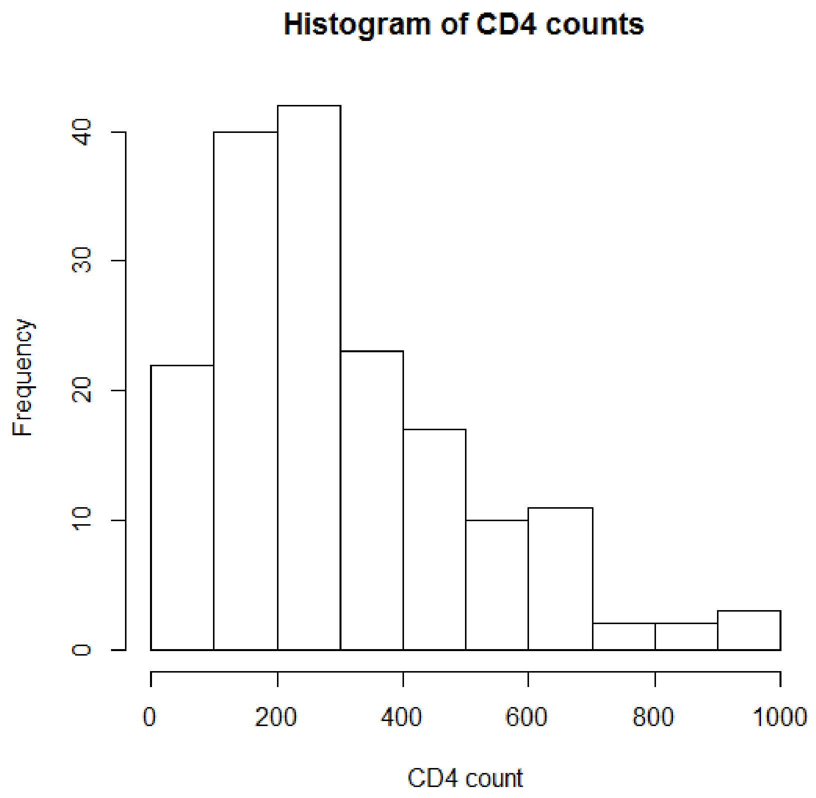
Purpose of last class's problem

- Get a first hand feel of defining and estimating variance-covariance matrices of a given data set
- Estimate the variance-covariance matrix under two *given* models of the data generating distribution
- Estimate the confidence intervals under each model

Data for our last in-class problem



Problem and model of the data

- **Objective**: Estimate the mean of the average CD4 count at the two time points of the *m* subjects in the study
- Simple linear model: $Y_{ij} = b_0 + Error_{ij}$
  - $mean(Error_{ij}) = 0$
- $Y = Xb_0 + Error$ – in matrix notation

How does *Y*, *X* and *Error* look like?

-
- $Y = \begin{bmatrix} Y_{11} \\ Y_{12} \\ Y_{21} \\ Y_{22} \\ \vdots \\ \vdots \\ Y_{m2} \end{bmatrix}$ $X = \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \\ \vdots \\ \vdots \\ 1 \end{bmatrix}$ $Error = \begin{bmatrix} e_{11} \\ e_{12} \\ e_{21} \\ e_{22} \\ \vdots \\ \vdots \\ e_{m2} \end{bmatrix}$

What are estimates of b_0 ?

-
- $\widehat{b_0} = \frac{\sum_{i=1}^{m} {(Y_{i1}+Y_{i2})}/{2}}{m} = \frac{\sum_{i=1}^{m}\sum_{j=1}^{2} Y_{ij}}{2m}$
- $Var(\widehat{b_0}) = (X^T X)^{-1} X^T V X (X^T X)^{-1}$
- $(X^T X) = 2m$
- *V* is the variance co-variance matrix

The Variance-Covariance of *Y*

$$
V(\mathbf{Y}) = \begin{bmatrix}
V_1 & 0 & 0 & 0 & \dots & 0 \\
0 & V_2 & 0 & 0 & \dots & 0 \\
0 & 0 & V_3 & 0 & \dots & 0 \\
. & . & . & & & . \\
. & . & . & & & . \\
. & . & . & & & . \\
0 & 0 & 0 & 0 & \dots & V_m
\end{bmatrix}
$$

The Variance-Covariance of $\mathbf{Y}_i$ - Most General

$$V_i = \begin{bmatrix} v_{i11} & v_{i12} & v_{i13} & v_{i14} \dots & v_{i1ni} \\ v_{i12} & v_{i22} & v_{i23} & v_{i24} \dots & v_{i2ni} \\ . & . & . & & . \\ . & . & . & & . \\ . & . & . & & . \\ v_{ini1} & v_{ini2} & v_{ini3} & \dots. & v_{inini} \end{bmatrix}$$

In our case, V_i based on two observations per subject

-

$$V_i = \begin{bmatrix} var(Y_{i1}) & cov(Y_{i1}, Y_{i2}) \\ cov(Y_{i1}, Y_{i2}) & var(Y_{i2}) \end{bmatrix}$$

$$Y_{ij} = b_0 + Error_{ij}$$

$$Error_{ij} = e_{ij}$$

Model I

$$Y_{ij} = b_0 + e_{ij}$$

e_{ij} independent, $E(e_{ij}) = 0, var(e_{ij}) = \sigma_e^2$

How would a picture of the model look like?

Model II

$$Y_{ij} = b_0 + Error_{ij}$$

$$Error_{ij} = b_{0i} + e_{ij}$$

$$Y_{ij} = b_0 + b_{0i} + e_{ij}$$

e_{ij} independent, $E(e_{ij}) = 0, var(e_{ij}) = \sigma_e^2$

b_{0i} independent, $E(b_{0i}) = 0, var(b_{0i}) = \sigma_b^2$

$cov(b_{0i}, e_{ij}) = 0.$

How would a picture of the model look like?

Useful formulae

- Given two random variables *A*, *B*
- $E[A+B] = E[A] + E[B]$
- $Var[A+B] = Var[A] + Var[B] + 2cov[A,B]$
- $cov[A,B] = E[AB] - E[A]E[B]$
- If *c* is a constant then $E[cA] = cE[A]$
- If *A* and *B* are independent then
  - $E[AB] = E[A]E[B]$

Under Model II, $var(Y_{i1})$

- $var(Y_{i1}) = var(b_0 + b_{0i} + e_{i1}) = \cdots$
- $var(b_0) + var(b_{0i}) + var(e_{i1}) + 2cov(b_0, b_{0i}) + 2cov(b_0, e_{i1}) + 2cov(b_{0i}, e_{i1}) = \cdots$

Under Model II, $cov(Y_{i1}, Y_{i2})$

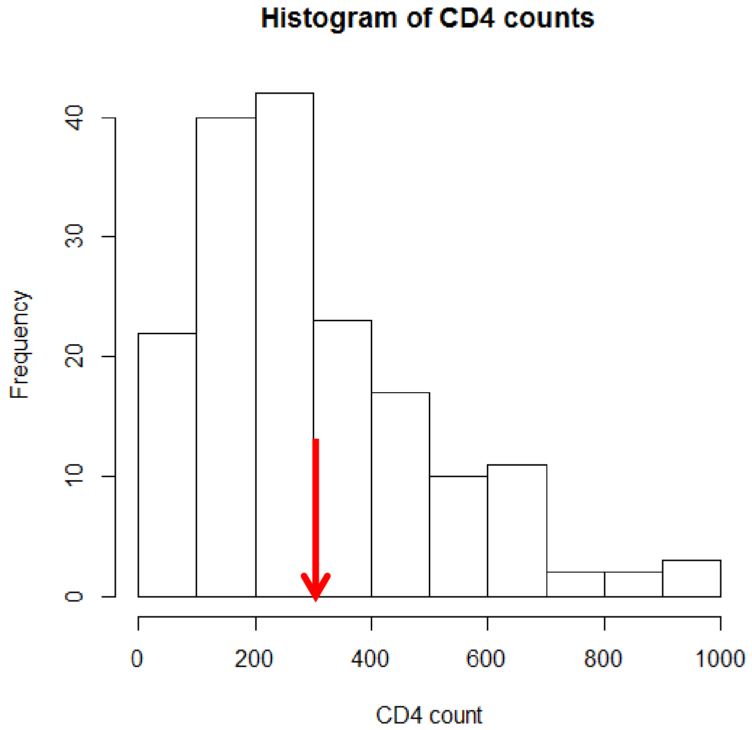
- $cov(Y_{i1}, Y_{i2}) = E[Y_{i1}Y_{i2}] - E[Y_{i1}]E[Y_{i2}]$
- $E[Y_{i1}] = E[b_0 + b_{0i} + e_{i1}] = E[b_0] + E[b_{0i}] + E[e_{i1}] = \ldots$
- $E[Y_{i1}Y_{i2}] = E[(b_0 + b_{0i} + e_{i1})(b_0 + b_{0i} + e_{i2})] = E\left[{b_0}^2 + 2b_0 b_{0i} + {b_{0i}}^2 + e_{i1}e_{i2} + b_{0i}e_{i1} + b_{0i}e_{i2}\right]$

Two V matrices under the two models would give standard error estimates

- $Var\left(\widehat{b_0}\right) = (X^TX)^{-1}X^TVX(X^TX)^{-1}$
- Model I $= \frac{{\sigma_e}^2}{2m}$ Estimated from sample variance
- Model II $= \frac{{\sigma_e}^2 + 2{\sigma_b}^2}{2m}$

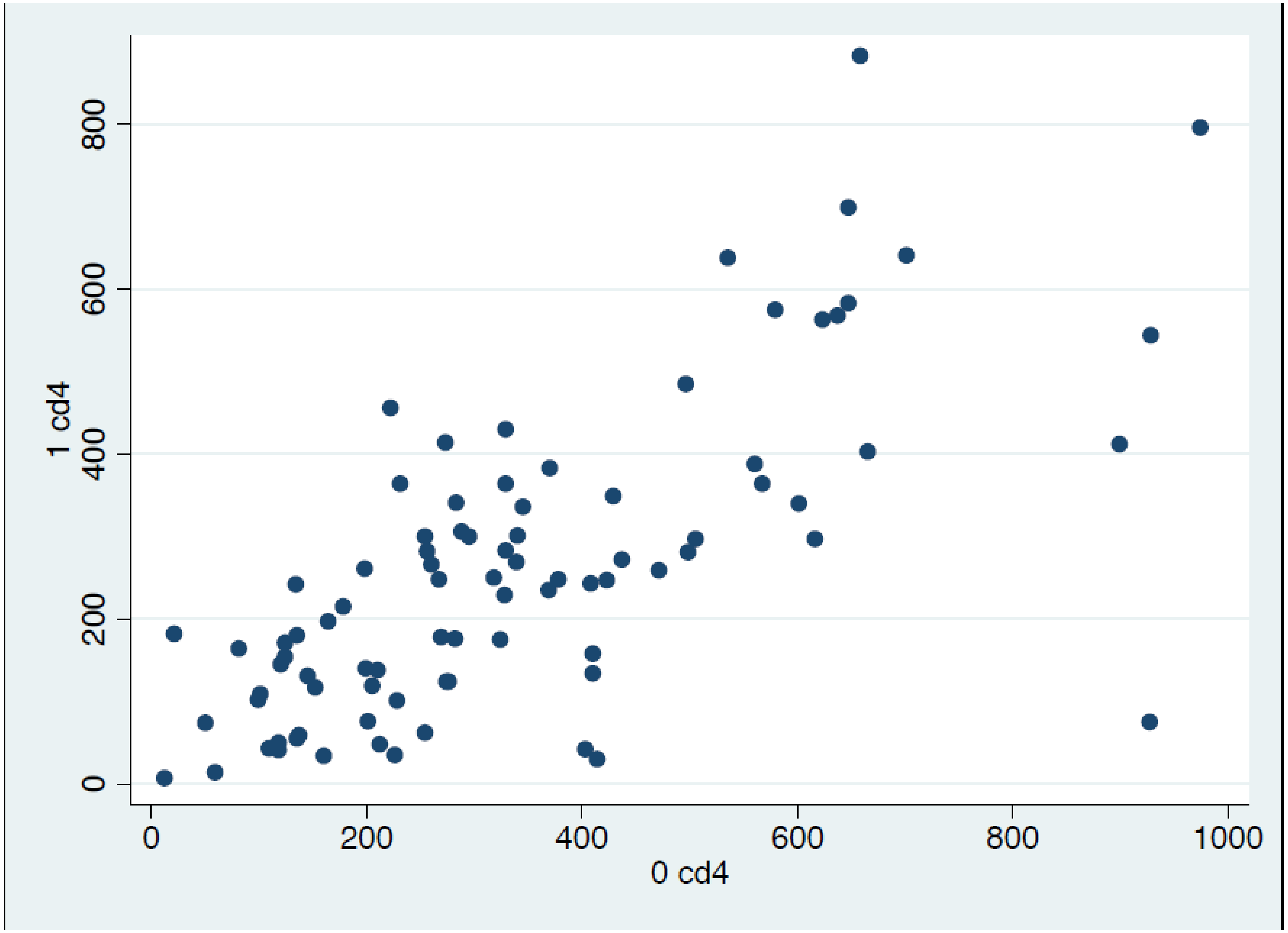
Estimated from sample co-variance

Results of estimates of b_0



- $\widehat{b_0}$=300.7
- SE$\left(\widehat{b_0}\right)$
  =15.7 Model I
  = 20.2 Model II
- Confidence intervals
  = $(270.0 - 331.4)$
  = $(261.0 - 340.4)$

What is a better model of the data?



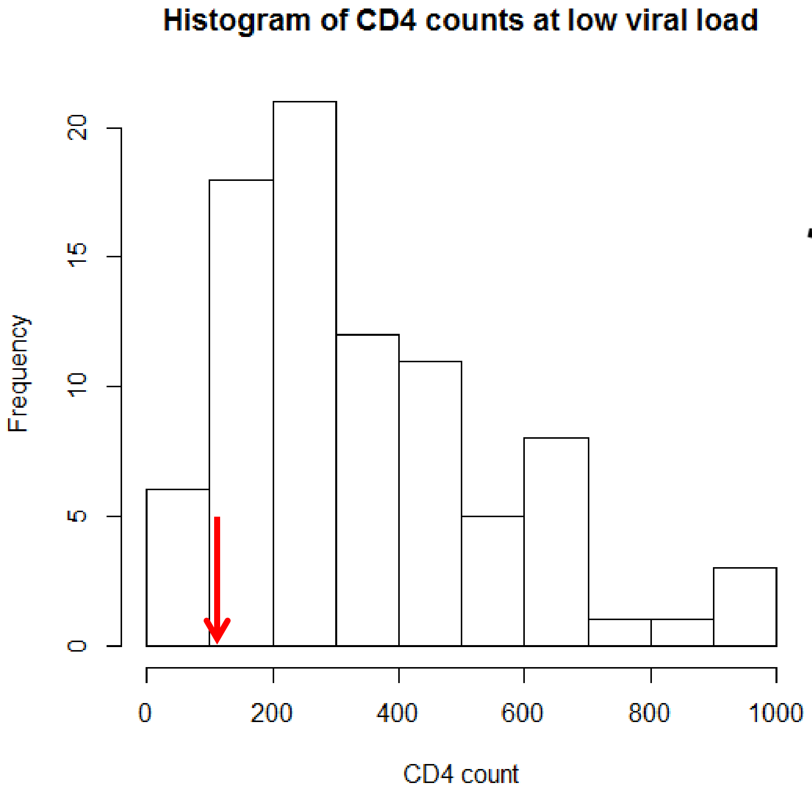
So far, to compute confidence interval of statistic (eg.mean)…

- We have assumed a model that allowed us to estimate the variance-covariance matrix
- We have good reasons to assume a probability distribution (Central Limit Theorem)

What if?

- Cannot get a good estimate the variance-covariance matrix
  - Not possible
  - You are lazy to go through the algebra
- Don’t have sufficient reason to assume a probability distribution of the statistic of interest

Estimate the 10th quantile of CD4 at low viral load



$$\widehat{q_{10}} = 118$$
$$SE\left(\widehat{q_{10}}\right) = ??$$

What does the standard error of a statistic supposed to represent?

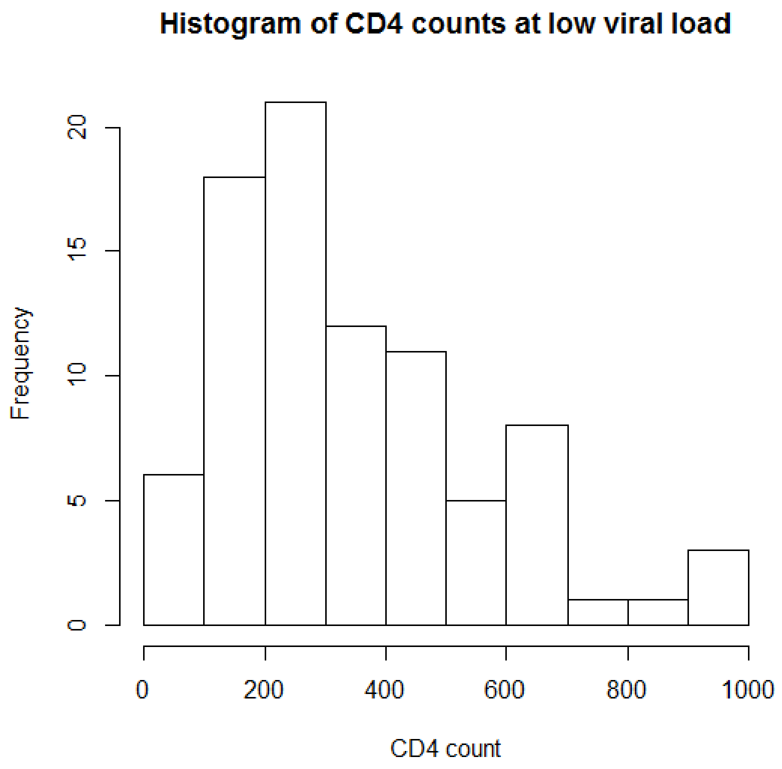
- The standard deviation of the estimates of this statistic in repeating experiments of the same kind
- The 10^{th} quantile was easy enough to compute for the data from our experiments
- What if we could repeat the experiments?

Approximations to the data generating distribution, $P_{Y.\theta}$

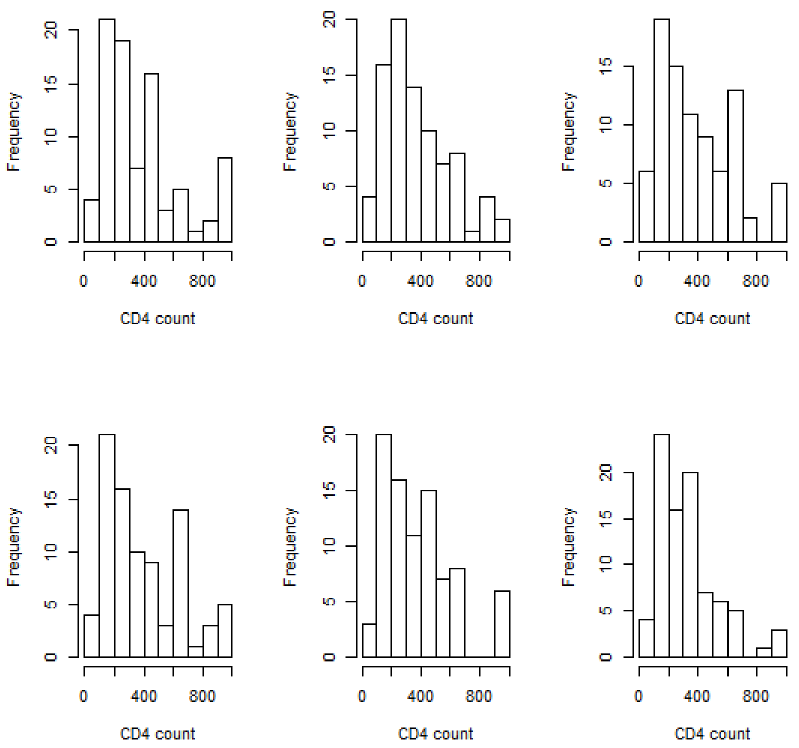
- Estimate θ by $\hat{\theta}$ using the data
  - $P_{Y,\hat{\theta}}$ approximates $P_{Y,\theta}$ (Parametric)
- The empirical distribution $\widehat{P^m}$ of the data approximates $P_{Y,\theta}$ (Non-parametric)

Data from repeated experiments

Original experiment data



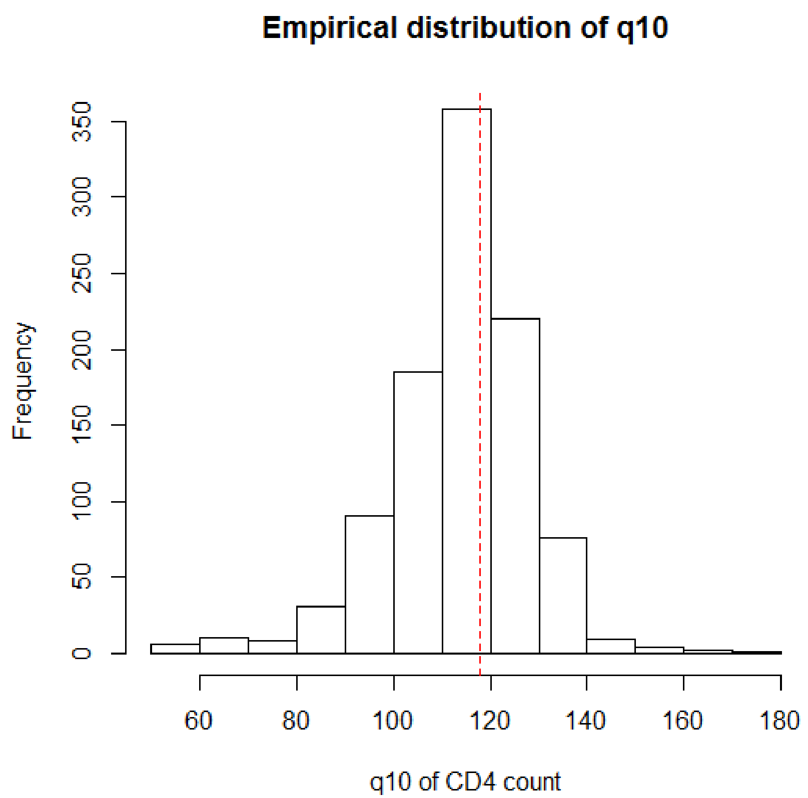
Repeated experiment data



Non-parametric bootstrap procedure

- Given data, Y from m subjects and statistic T (eg. q_{10}) of interest
- Repeat B times
  - Generate a new data set, $\tilde{Y}$ by drawing m subjects **with replacement**
  - Compute the statistic of interest, $\tilde{T}$
- Estimate the sampling distribution of T from the empirical distribution of $\tilde{T}$

Empirical distribution of $\widehat{q_{10}}$ based on 1000 bootstrap experiments



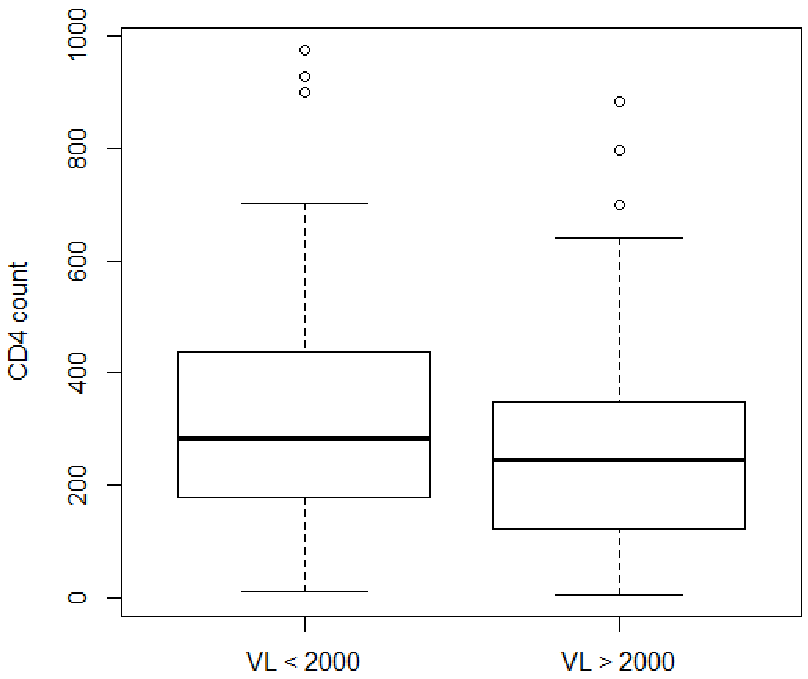
95% CI based on 2.5% and 97.5% quantiles of sampling distribution: (81-136)

Important consideration for longitudinal data

- Bootstrap procedure must respect the dependence relationships between observations
  - Clustering Bootstrap procedure

What is the effect of viral load on CD4 count?

Simple linear model: $Y_{ij} = b_0 + b_1(VL > 2000) + e_{ij}$

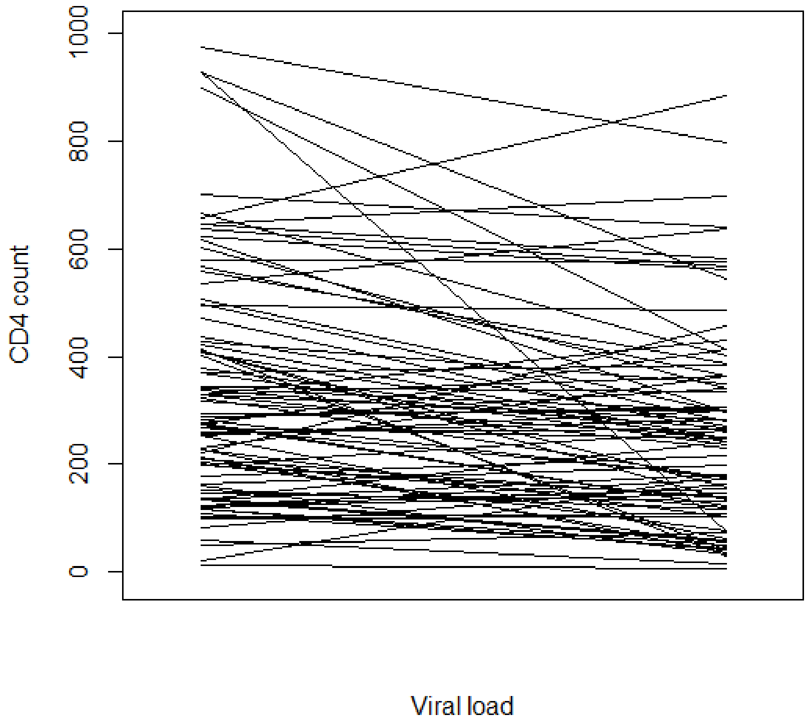


We would like to estimate $SE(b_1)$

Options to estimate a confidence interval $SE(b_1)$

- Assume a model like Model II of our in-class problem
  - Estimate V
  - $Var(\widehat{b_0}) = (X^T X)^{-1} X^T V X (X^T X)^{-1}$
- Reduce model assumptions by not explicitly modeling the variance and covariance by a boostrapping procedure

Would you bootstrap observations?



Standard linear regression

```
. regress cd4 medvl

      Source |       SS       df       MS              Number of obs =     172
-------------+------------------------------           F(  1,   170) =    6.76
       Model |  276080.703     1  276080.703           Prob > F      =  0.0101
    Residual |  6944087.97   170  40847.5763           R-squared     =  0.0382
-------------+------------------------------           Adj R-squared =  0.0326
       Total |  7220168.67   171  42223.2086           Root MSE      =  202.11

------------------------------------------------------------------------------
         cd4 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       medvl |  -80.12791   30.82116    -2.60   0.010    -140.9694   -19.28643
       _cons |   340.7558   21.79385    15.64   0.000     297.7344    383.7772
------------------------------------------------------------------------------
```

Linear Mixed Effects Regression

```
. xtmixed cd4 medvl || id:
```

```
Mixed-effects ML regression                     Number of obs      =       172
Group variable: id                              Number of groups   =        86

                                                Obs per group: min =         2
                                                               avg =       2.0
                                                               max =         2


                                                Wald chi2(1)       =     22.27
Log likelihood = -1128.0325                     Prob > chi2        =    0.0000
```

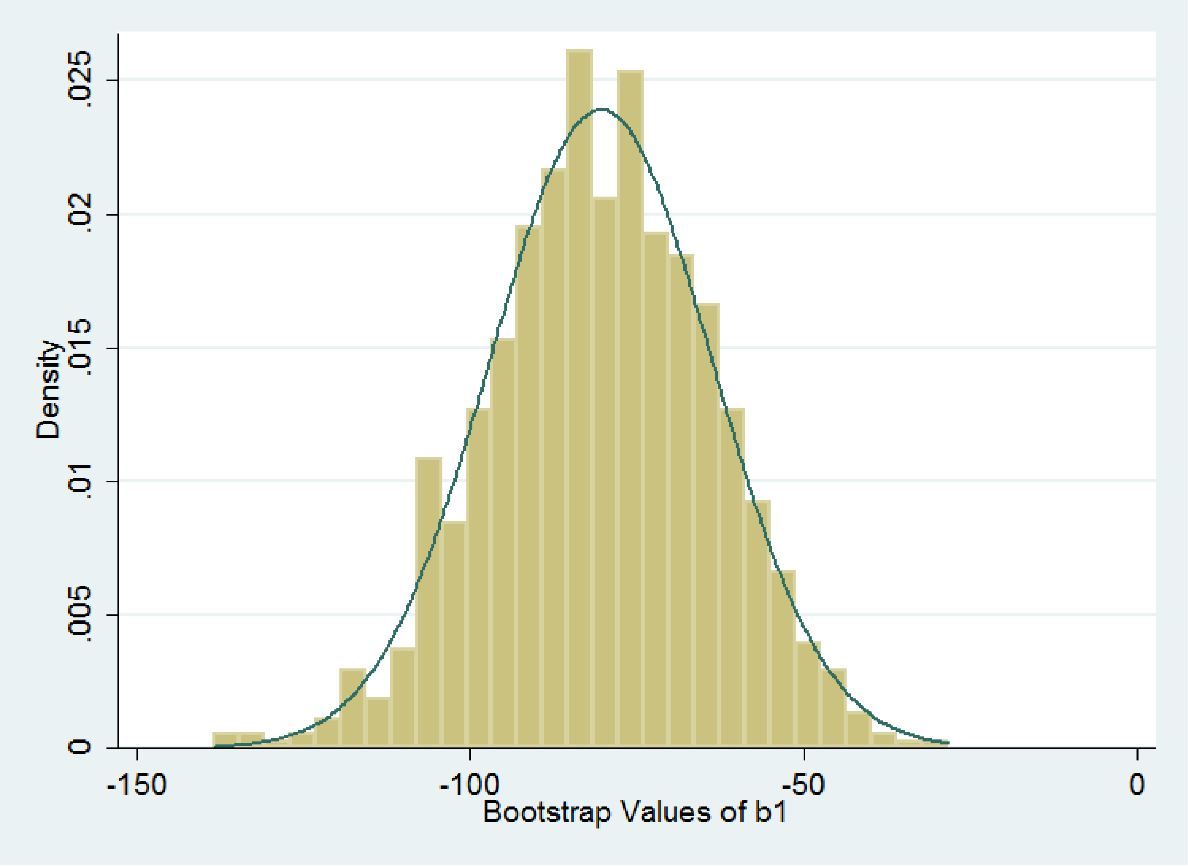
cd4	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
medvl	-80.12791	16.97926	-4.72	0.000	-113.4066	-46.84917
_cons	340.7558	21.66677	15.73	0.000	298.2897	383.2219

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
id: Identity				
sd(_cons)	167.26	15.8333	138.9361	201.3582
sd(Residual)	111.3404	8.489627	95.88472	129.2875

Clustered Bootstrap of standard linear regressions

```
. bootstrap, saving(bootout) reps(1000) cluster(id): regress cd4 medvl
(running regress on estimation sample)

Bootstrap replications (1000)
----+--- 1 ---+--- 2 ---+--- 3 ---+--- 4 ---+--- 5
..................................................    50
..................................................   100
..................................................   150

..................................................   900
..................................................   950
..................................................  1000

Linear regression                               Number of obs      =       172
                                                Replications       =      1000
                                                Wald chi2(1)       =     21.72
                                                Prob > chi2        =    0.0000
                                                R-squared          =    0.0382
                                                Adj R-squared      =    0.0326
                                                Root MSE           =  202.1078

                                  (Replications based on 86 clusters in id)
------------------------------------------------------------------------------
             |   Observed   Bootstrap                         Normal-based
         cd4 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       medvl |  -80.12791    17.19242    -4.66   0.000    -113.8244   -46.43138
       _cons |   340.7558    22.89867    14.88   0.000     295.8752    385.6364
------------------------------------------------------------------------------
```

Sampling distribution of b_1



Quick Summary of Repeated Measures Strategies

- Transition Models Relies on some assumption of conditional independence of repeated outcomes, by adjusting for previous outcome value: $E(Y_{ij}|X_{ij}, Y_{i(j-1)})$.

- Mixed Effects Models – explicit model of sources of random variability at cluster level, $E(Y_{ij}|X_{ij},\alpha_i)$, $\alpha_i \sim N(0,\sigma^2_{\alpha}),\ldots.$

- Generalized Estimating Equation (GEE) approach – only specify relative simple parameters (e.g., $E(Y_{ij}|X_{ij})$).

Example: observations within subjects: The Effect of Drug and Alcohol Use on Teenage Sexual Activity

- Minnis & Padian (2001) conducted a longitudinal study of teenagers in San Rafael, California to investigate the association between drug and alcohol use and sexual activity on the same day.

- Participants were asked to keep track of their activities over approximately one month and binary indicator variables were created to show whether drug/alcohol use and/or sexual activity were reported for each 24 hour period.

Example of Binary Outcome: Sex, Drugs and Teenagers

- A longitudinal study of the effects of drug-use on sexual activity.

- Let X_{ij}, the only explanatory variable of interest for now, indicate whether or not subject i reported drug-use (1=yes, 0=no) on day j.

- Let Y_{ij} denote whether subject had sex (1=yes, 0=no), i.e., Y_{ij} is a binary outcome and thus its expectation can be modeled via the logit transform.

Data

	eid	today	drgalcoh	sx24hrs
1.	10122	03 Jun 98	yes	no
2.	10123	04 Jun 98	no	no
3.	10123	05 Jun 98	no	no
4.	10123	06 Jun 98	yes	no
5.	10123	07 Jun 98	no	no
6.	10123	08 Jun 98	no	no
7.	10123	09 Jun 98	no	no
8.	10123	12 Jun 98	no	no
9.	10123	14 Jun 98	yes	no
10.	10123	16 Jun 98	no	no
11.	10123	17 Jun 98	no	no
12.	10123	18 Jun 98	no	yes
13.	10123	19 Jun 98	no	no
14.	10123	20 Jun 98	no	no
15.	10123	21 Jun 98	no	no
16.	10123	23 Jun 98	no	no
17.	10123	25 Jun 98	no	yes
18.	10123	28 Jun 98	no	no
19.	10123	29 Jun 98	no	yes
20.	10123	01 Jul 98	no	yes
21.	10123	02 Jul 98	no	no
22.	10123	03 Jul 98	no	no
23.	10123	04 Jul 98	no	no
24.	10123	05 Jul 98	no	no
25.	10124	04 Jun 98	no	no
26.	10124	07 Jun 98	no	no
27.	10124	08 Jun 98	no	no

Transition Model for Teenage Sex and Drug-Use

- For time-sequenced repeated measures, build the joint distribution by specifying a sequence of distributions that are conditioned on previous measurements on the individual. These are called transition (Markov) models.

- For the study of teenage sex:

$$\text{logit}[P(Y_{ij}=1 \mid \mathrm{X_{ij}} = \mathrm{x_{ij}}, Y_{ij-1}, Y_{ij-2}, \ldots, Y_{i1})] = \beta_0^{\mathrm{TM}} + \beta_1^{\mathrm{TM}} \mathrm{x_{ij}} + \delta Y_{ij-1}$$

- where Y_{i1} is outcome at time t_{i1}, Y_{i2} at t_{i2}, ..., and $t_{i1} < t_{i2} < \ldots < t_{in_i}$.

Transition Model for Teenage Sex and Drug-Use

- This approach constructs the likelihood, for the case of this model

$$\text{logit}[P(Y_{ij}=1 \mid X_{ij}=x_{ij}, Y_{ij-1}, Y_{ij-2}, \ldots, Y_{i1})] = \beta_0^{\text{TM}} + \beta_1^{\text{TM}} \mathrm{x}_{\mathrm{ij}} + \delta Y_{ij-1}$$

- under the assumption that:

$$Y_{ij} \perp (Y_{ij-2,} Y_{\mathrm{ij}\text{-}3,}, \ldots, Y_{\mathrm{i}1}) \mid X_{ij}, Y_{ij-1}$$

Transition Models

- $exp(\delta)$ = odds ratio (OR) of among subjects who did versus did not have sex during the prior day, keeping drug status fixed.
- $\exp(\beta_1^{TM})$ = OR of drug use vs. not for either subjects who reported having sex or did not have sex the previous day.
- use generalized linear models (glm) software (e.g., linear, logistic, poisson regression).
- Most commonly used for nice, time-structured data.

Sexual Activity and drug/alcohol use among teenagers revisted

Main Variables

sex24hrs - sex in last 24 hrs. (0=no, 1=yes)

drgalcoh - drug or alcohol use in last 24 hrs.

tues-sun - dummy variables designating day of week

Results using xtgee in STATA

.sort eid today

*** This is how one puts Y_{ij-1} onto same line as Y_{ij} to be used as covariate**

.by eid: gen sxyest = sx24hrs[_n-1]

.by eid: replace sxyest = . if _n==1

```
.logistic sx24hrs drgalcoh sxyest

. Logit estimates                                     Number of obs   =       1607
                                                    LR chi2(2)      =      55.39
                                                    Prob > chi2     =     0.0000
Log likelihood = -942.60915                         Pseudo R2       =     0.0285

------------------------------------------------------------------------------
     sx24hrs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
exp(β1™)drgalcoh 1.63798   .1986677     4.07   0.000     1.291421     2.07754
exp(δ)      sxyes 2.051903  .2478562     5.95   0.000     1.619338     2.600018
------------------------------------------------------------------------------
```

Random Effects Models

- Uses a random effect to model the relative similarity of observations made on same statistical unit (e.g., person)

- Assumes Y_{ij} and Y_{ik}, $j \neq k$ are independent given some realized value of a random effect (β_{i0}) and the covariates.

$$Y_{ij} \perp Y_{ik} \mid X_{ij}, \beta_{0i}$$

- The model assumes these random effects are randomly drawn from a known distribution.

Random Effects Model for Teenage Sex and Drug-Use

$$\operatorname{logit}[P(Y_{ij}=1 \mid \beta_{0i}, X_{ij}=x_{ij})] = \log\left(\frac{P(Y_{ij}=1 \mid \beta_{0i}, X_{ij}=x_{ij})}{P(Y_{ij}=0 \mid \beta_{0i}, X_{ij}=x_{ij})}\right) = \beta_0^{RE} + \beta_{0i} + \beta_1^{RE} x_{ij}$$

- Assume that the repeated observations for the ith teenager are independent of one another given β_{i0} and X_{ij}.

- Must assume parametric distribution for the β_{i0} , usually $\beta_{i0} \sim N(0, \tau^2)$.

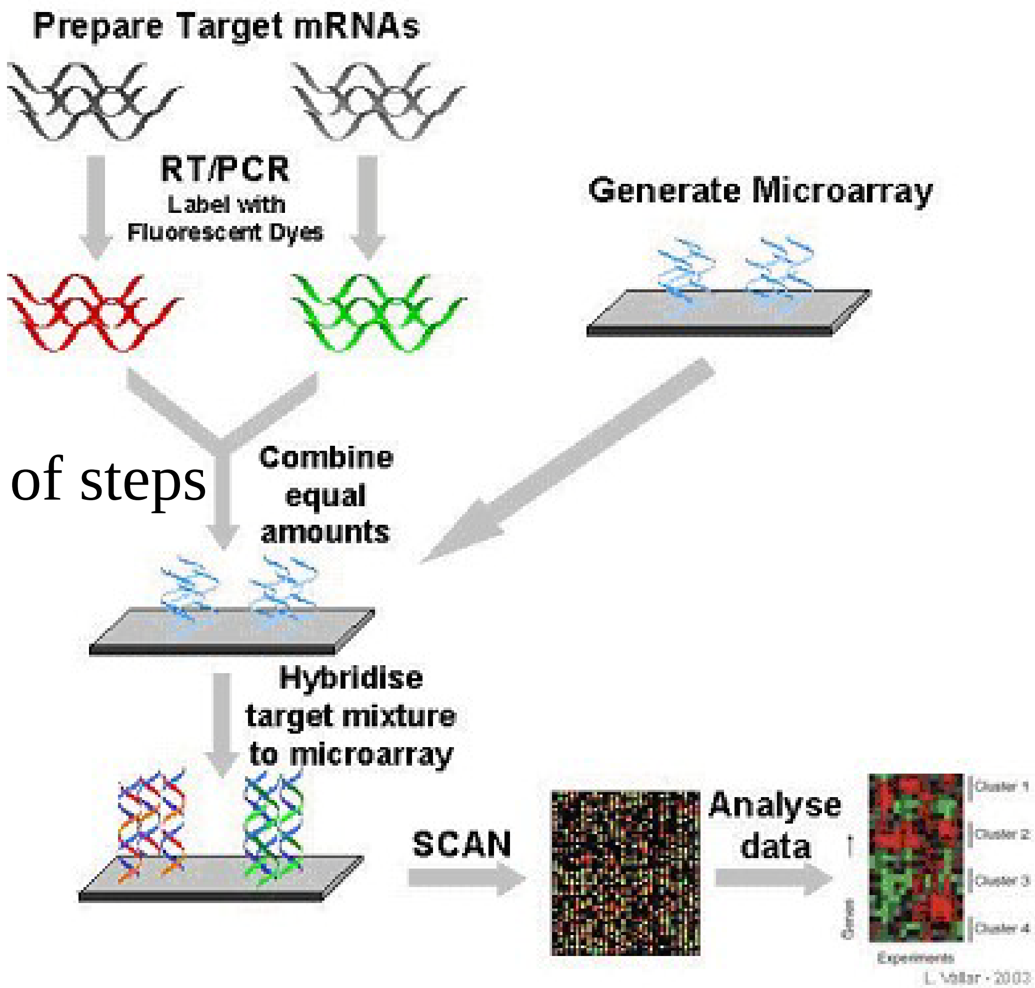
- $exp(\beta_1^{RE})$ is odds ratio for having sex when subject *i* reports drug-use relative to when same subject does not report drug-use.

Motivation for This Approach

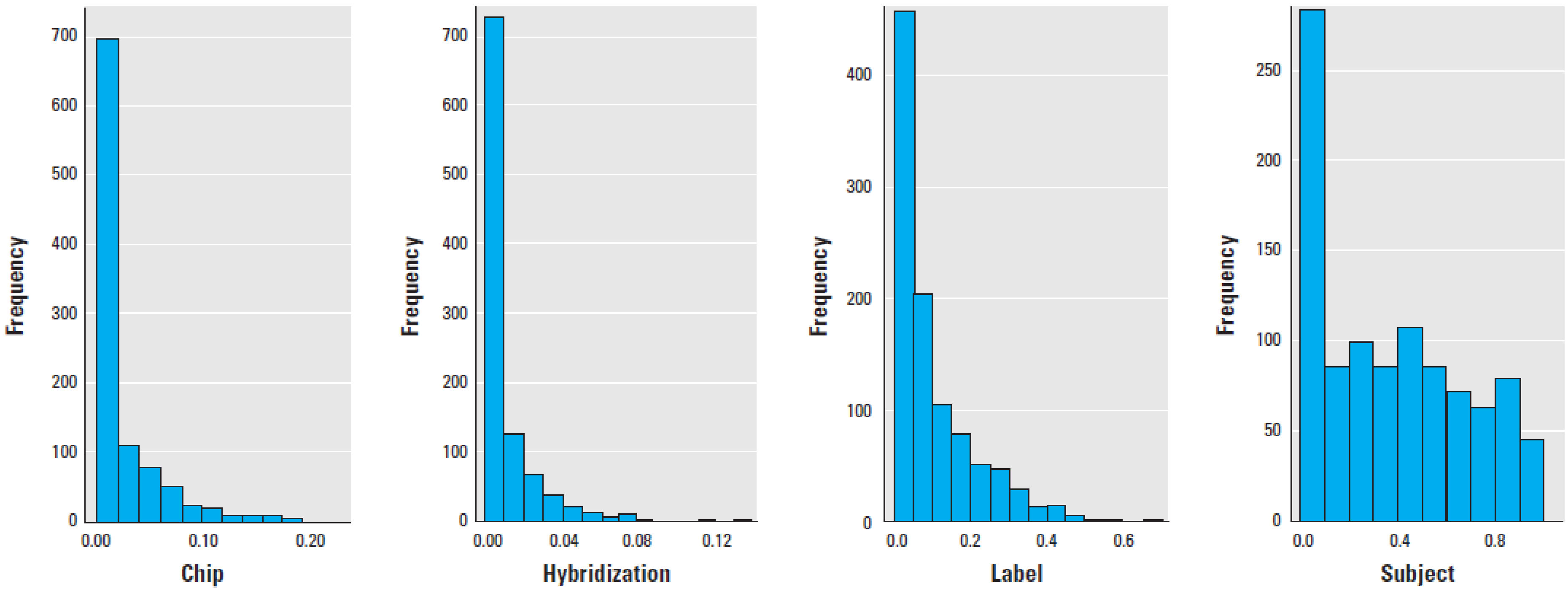
- Natural for modeling heterogeneity across individuals in their regression coefficients.
- This heterogeneity can be represented by a probability distribution
- Most useful when object is to make inferences about individuals rather than population averages.

Understanding sources of experimental variation in microarray measurements

Hierarchy of steps



Distribution of intra-class coefficients



Dose-dependent effect of benzene exposure on gene expression

McHale et al 2011

Motivation for This Approach

- Also useful to estimate the contributions to variability from different sources (e.g., within and among individuals).

- Can be extended to hierarchy of units (multi-level modeling), such as repeated longitudinal measures of a person, within a household, within a community .....

Some available software for random effects models

- Linear Models
  - Proc Mixed in SAS
  - xtreg in STATA (only simple random effects models)
  - xtmixed in STATA 10
  - lme in R

- Logistic and Poisson Models
  - xtlogit and xtpoisson in STATA for simple random effects, xtmelogit and xtmepoisson for general mixed models in STATA version 10
  - gllamm – for general mixed models is STATA add-on

Random effects using xtlogit in STATA

```
. xtlogit sx24hrs drgalcoh, or i(eid) re

Random-effects logit                            Number of obs      =      1708
Group variable (i) : eid                        Number of groups   =       109

Random effects u_i ~ Gaussian                   Obs per group: min =         1
                                                               avg =      15.7
                                                               max =        33

                                                Wald chi2(1)       =      5.48
Log likelihood  = -921.39213                    Prob > chi2        =    0.0192
```

sx24hrs	OR	Std. Err.	z	P>|z|	[95% Conf.	Interval]
$\exp(\beta_1^{RE})$	1.447266	.2284893	2.34	0.019	1.062096	1.972119
/lnsig2u	.5483488	.2428238			.0724228	1.024275
τ sigma_u	1.315444	.1597106			1.036875	1.668854
rho	.3446819	.0166718			.2463036	.4584528

```
Likelihood ratio test of rho=0: chibar2(01) =   184.17 Prob >= chibar2 = 0.000
```

Estimation of Marginal Models (GEE)

- Estimate marginal mean model.
- Marginal model is a population, not individual, model.
- The marginal $E[Y_{ij} \mid X_{ij} = x_{ij}]$ is defined as the mean value of an observation Y_{ij} in the theoretical experiment where one randomly draws an observation from a population where everyone has $X_{ij} = x_{ij}$.

Marginal Models (GEE)

- For instance, if Y_{ij} is the cholesterol and X_{ij} = *yes* if one smokes, *no* otherwise. In a marginal model, $E[Y_{ij} \mid X_{ij} = yes]$ will be the mean of a randomly drawn Y_{ij} from the sub-population where everyone smokes.

Connection between Mixed Models and GEE – Example 1 from Chapter 5

Two kinds of people in a target population whose members gets exposed to E and does not get exposed to E

$$(b_0 = 0, b_1 = 4)$$

$$\log\{\Pr(Y_{ij} = 1 | b_{0i} = -2.996, X_{ij} = x_{ij})\} = b_0 - 2.996 + b_1 x_{ij}$$
$$\log\{\Pr(Y_{ij} = 1 | b_{0i} = -1.609, X_{ij} = x_{ij})\} = b_0 - 1.609 + b_1 x_{ij}.$$

Connection between Mixed Models and GEE – Example 2 from Chapter 5

Two kinds of people in a target population whose members gets exposed to E and does not get exposed to E..

$$(b_0 = 0, b_1 = 4)$$

$$\text{logit}\{\Pr(Y_{ij} = 1 | b_{0i} = -1.386, X_{ij} = x_{ij})\} = b_0 - 1.386 + b_1 x_{ij}$$

$$\text{logit}\{\Pr(Y_{ij} = 1 | b_{0i} = 0, X_{ij} = x_{ij})\} = b_0 + 0 + b_1 x_{ij},$$

Parameter Interpretation in a marginal model

- Parameters in an equivalent random effects and GEE model have subtly different interpretations.

- Coefficients in a random effects model represent expected differences (odds ratios, relative risks, etc) within an individual, given a change in their *X* from one value to another

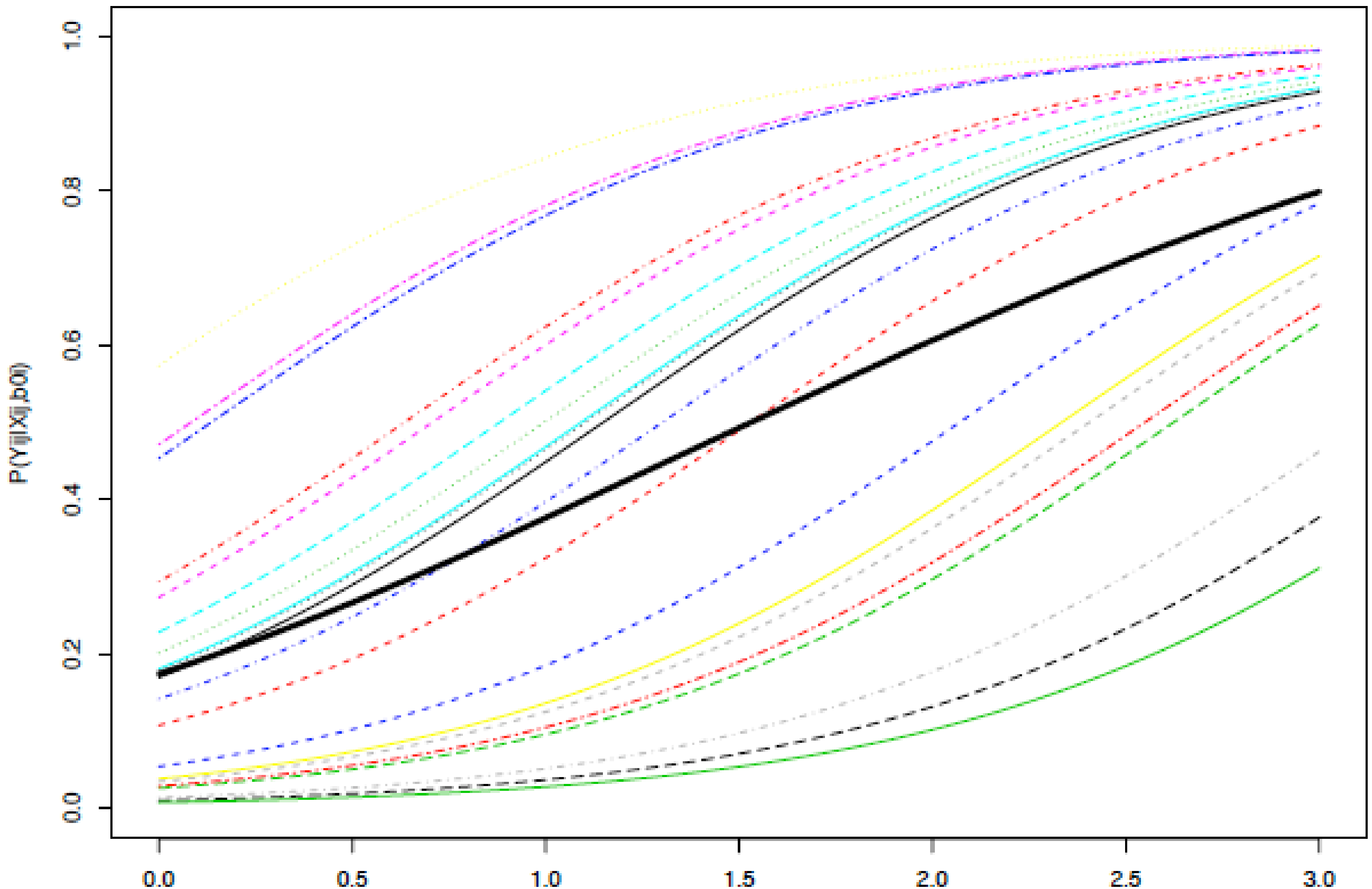
- Coefficients in a marginal model represent expected differences (odds ratios, relative risks, etc) within an population, given a change in everyone's *X* from one value to another.

Parameter Interpretation in a GEE model, cont.

- In linear, log-linear models, the random effects and marginal regression parameters are the same.

- In Logistic regression, they are different – more later.

Figure 5.1: DIFFERENCE BETWEEN SUBJECT-SPECIFIC LOGISTIC REGRESSIONS AND MARGINAL VERSION: THE INDIVIDUAL THIN LINES REPRESENT CURVES FOR DIFFERENT INDIVIDUALS - THE THICK BLACK LINE REPRESENTS THE MARGINAL PROBABILITY OF DISEASE, AVERAGED OVER THE INDIVIDUAL CURVES



Marginal Models (GEE)

- GEE software typically allows several different "working" correlation models (e.g., exchangeable, auto-regressive, unstructured, etc.).

- These correlation models are used to build weight matrices, which are used in a weighted regression.

- When deriving inferences for the coefficients, though, it calculates "robust" standard errors.

Examples of Correlation Models

$$V = \sigma^2 \left[\begin{array}{ccccc} R_{01} & 0 & 0 & \cdots & 0 \\ 0 & R_{02} & 0 & \cdots & 0 \\ 0 & 0 & R_{03} & \cdots & 0 \\ 0 & 0 & 0 & \cdots & 0 \\ 0 & 0 & 0 & \cdots & R_{0n} \end{array} \right.$$

- Each individual is independent of all others
- Correlation within individuals across longitudinal observations has the same structure

Structure for R_0

- General structure:

$$R_0 = \begin{bmatrix} 1 & \rho_{12} & \rho_{13} & \cdots & \rho_{1n} \\ \rho_{12} & 1 & \rho_{23} & \cdots & \rho_{2n} \\ \rho_{13} & \rho_{23} & 1 & \cdots & \rho_{3n} \\ \vdots & \vdots & \vdots & 1 & \vdots \\ \rho_{1n} & \rho_{2n} & \rho_{3n} & \cdots & 1 \end{bmatrix}$$

- A lot of unknown parameters

Correlation Models (contd): Uniform correlation (compound symmetry or exchangeable)

$$R_0 = \begin{bmatrix} 1 & \rho & \rho & \cdots & \rho \\ \rho & 1 & \rho & \cdots & \rho \\ \rho & \rho & 1 & \cdots & \rho \\ \vdots & \vdots & \vdots & 1 & \vdots \\ \rho & \rho & \rho & \cdots & 1 \end{bmatrix}$$

- Arises from random effects model

$$Y_{ij} = \alpha + \alpha_i + \beta x_{ij} + e_{ij}$$

Errors e_{ij} uncorrelated, and independent of x_{ij} and α_i

$$\rho = \frac{Var(\alpha_i)}{Var(\alpha_i) + Var(e_{ij})}$$

Correlation Models (contd):Time-Decaying Correlations (Auto-regressive)

$$R_0 = \begin{bmatrix} 1 & \rho & \rho^2 & \cdots & \rho^{n-1} \\ \rho & 1 & \rho & \cdots & \rho^{n-2} \\ \rho^2 & \rho & 1 & \cdots & \rho^{n-3} \\ \vdots & \vdots & \vdots & 1 & \vdots \\ \rho^{n-1} & \rho^{n-2} & \rho^{n-3} & \cdots & 1 \end{bmatrix}$$

Auto-regressive: $e_{ij} = \rho e_{ij-1} + \eta_{ij}$

Not great for unequally spaced longitudinal data

Exponential correlation model generalizes this to $\mathrm{corr}(y_{ij}, y_{ik}) = \rho^{|t_j - t_k|}$ rather than $\rho^{|j-k|}$

Examples of var-cov. models

Description	Abbrev.	Var-Cov. Matrix
Compound Symmetry	CS	$\begin{matrix} \sigma^2+\sigma_0^2 & \sigma_0^2 & \sigma_0^2 & \sigma_0^2 \\ \sigma_0^2 & \sigma^2+\sigma_0^2 & \sigma_0^2 & \sigma_0^2 \\ \sigma_0^2 & \sigma_0^2 & \sigma^2+\sigma_0^2 & \sigma_0^2 \\ \sigma_0^2 & \sigma_0^2 & \sigma_0^2 & \sigma^2+\sigma_0^2 \end{matrix}$
Unstructured	UN	$\begin{matrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} \\ \sigma_{12} & \sigma_2^2 & \sigma_{23} & \sigma_{24} \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 & \sigma_{34} \\ \sigma_{14} & \sigma_{24} & \sigma_{34} & \sigma_4^2 \end{matrix}$
Autoregressive	AR(1)	$\begin{matrix} \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 & \rho^3\sigma^2 \\ \rho\sigma^2 & \sigma^2 & \rho\sigma^2 & \rho^2\sigma^2 \\ \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 & \rho\sigma^2 \\ \rho^3\sigma^2 & \rho^2\sigma^2 & \rho\sigma^2 & \sigma^2 \end{matrix}$
Banded Diagnonal	UN(1)	$\begin{matrix} \sigma_1^2 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 \\ 0 & 0 & 0 & \sigma_4^2 \end{matrix}$
Spatial Power	SP(POW)(c)	$\begin{matrix} \sigma^2 & \rho^{d12}\sigma^2 & \rho^{d13}\sigma^2 & \rho^{d14}\sigma^2 \\ \rho^{d12}\sigma^2 & \sigma^2 & \rho^{d23}\sigma^2 & \rho^{d24}\sigma^2 \\ \rho^{d13}\sigma^2 & \rho^{d23}\sigma^2 & \sigma^2 & \rho^{d34}\sigma^2 \\ \rho^{d14}\sigma^2 & \rho^{d24}\sigma^2 & \rho^{d34}\sigma^2 & \sigma^2 \end{matrix}$

The GEE Algorithm

- Algorithm is similar to the one used for the non-repeated measures problems (e.g., OLS for continuous data, logistic regression for binary and Poisson regression for counts).

- Let $R(\alpha)$ be a n_i x n_i "working" correlation matrix that is fully characterized by a vector of parameters, α.

- V_i is again the variance-covariance of the observations which will be a function of the mean ($E(Y_i|X_i)$), a scale parameter, ϕ and $R(\alpha)$.

Standard Errors of Coefficients

- GEE will normally return two estimates of the variance of the coefficient estimates, 1) naive and 2) robust.

- Naive assumes that the chosen model for $R(\alpha)$, such as compound symmetry, is correct.

- Robust is a more nonparametric estimate that does not assume your guess for $R(\alpha)$ is correct. However, its variance estimates can be more variable.

GEE Marginal Model for Teenage Sex and Drug-Use

$$\operatorname{logit}[P(Y_{ij}=1 \mid X_{ij}=x_{ij})] = \log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = \log\left(\frac{P(Y_{ij}=1 \mid X_{ij}=x_{ij})}{P(Y_{ij}=0 \mid X_{ij}=x_{ij})}\right) = \beta_0^M + \beta_1^M x_{ij}$$

- *var*(Y_{ij})= μ_{ij} (1-μ_{ij})*, *corr*(Y_{ij}, Y_{ik}) = ρ (i.e., assume compound symmetry).
- *exp*(β_1^M) is a ratio of population frequencies, i.e., it is a population averaged parameter. It is the odds ratio of the probabilities (proportions) of teenagers who would engage in sexual activity in populations reporting drug use vs. populations not reporting drug-use.
- * Semi-robust inference – can you tell why?

Sexual Activity and drug/alcohol use among teenagers revisted

Main Variables

sex24hrs - sex in last 24 hrs. (0=no, 1=yes)

drgalcoh - drug or alcohol use in last 24 hrs.

tues-sun - dummy variables designating day of week

Results using xtgee in STATA

robust SE

```
. xtgee sx24hrs drgalcoh, eform i(id) family(binomial) cor(ind) robust

GEE population-averaged model                   Number of obs      =      1708
Group variable:                         id      Number of groups   =       109
Link:                                logit      Obs per group: min =         1
Family:                           binomial                     avg =      15.7
Correlation:                   independent                     max =        33

                               (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |             Semi-robust
     sx24hrs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
exp(β1M)drgalcoh 1.739521   .3149874     3.06   0.002     1.219823    2.480635
------------------------------------------------------------------------------
```

non-robust (naive) SE

```
. xtgee sx24hrs drgalcoh, eform i(eid) family(binomial) cor(ind)

------------------------------------------------------------------------------
     sx24hrs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    drgalcoh |   1.739521     .20244     4.76   0.000     1.384744    2.185194
------------------------------------------------------------------------------
```

xtgee Options

- family(?), link(?) -- identify that we wish linear regression with continuous outcome (as compared to, say, binary outcomes – more later)
- corr(ind) -- identify that we will assume independence for our correlation structure (some other possibilities include exchangeability and autoregressive structures)
- i(?)--identify which variable indentifies the individual (or cluster)
- ro -- identifies that we wish robust estimates of variability

Model 2 – same marginal model, different working correlation.

$$\log it[P(Y_{ij}=1 \mid X_{ij}=x_{ij})] = \log\left(\frac{\mu_{ij}}{1-\mu_{ij}}\right) = \log\left(\frac{P(Y_{ij}=1 \mid X_{ij}=x_{ij})}{P(Y_{ij}=0 \mid X_{ij}=x_{ij})}\right) = \beta_0^M + \beta_1^M x_{ij}$$

x_{ij} = 0 if drug/alcohol use is no, 1 if yes

y_{ij} = 0 if no sex in last 24 hours, 1 if yes

$cor(Y_{ij}, Y_{ij'}) = \rho$ (<u>compound symmetry</u> or <u>exchangeable</u> correlation structure)

Results of Model 2 using STATA

robust SE

```
. xtgee sx24hrs drgalcoh, eform i(id) family(binomial) cor(exc) robust

GEE population-averaged model                   Number of obs      =      1708
Group variable:                         id      Number of groups   =       109
Link:                                logit      Obs per group: min =         1
Family:                           binomial                     avg =      15.7
Correlation:                  exchangeable                     max =        33
                               (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |             Semi-robust
     sx24hrs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    drgalcoh |   1.393705   .1919735     2.41   0.016     1.063956    1.825653
------------------------------------------------------------------------------
```

non-robust (naive) SE

```
. xtgee sx24hrs drgalcoh, eform i(eid) family(binomial) cor(exc)
------------------------------------------------------------------------------
     sx24hrs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    drgalcoh |   1.393705   .1701631     2.72   0.007     1.097095    1.770507
------------------------------------------------------------------------------
```

Estimated Working Correlation

```
. xtcorr
```

	c1	c2	c3	c4	c5	c6	c7	c8	c9
r1	1.0000								
r2	0.1614	1.0000							
r3	0.1614	0.1614	1.0000						
r4	0.1614	0.1614	0.1614	1.0000					
r5	0.1614	0.1614	0.1614	0.1614	1.0000				
r6	0.1614	0.1614	0.1614	0.1614	0.1614	1.0000			
r7	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	1.0000		
r8	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	1.0000	
r9	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	1.0000
r10	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r11	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r12	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r13	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r14	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r15	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r16	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r17	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r18	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614
r19	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614	0.1614

Model 3 – adjusting for day of week

$$\log it[P(Y_{ij}=1 \mid x_{ij}, day_{ij})] = \beta_0 + \beta_1 x_{ij} + \gamma_1 z_{1ij} + \gamma_2 z_{2ij} + \cdots + \gamma_6 z_{6ij}$$

x_{ij} = 1 if drug/alcohol use is yes, 0 if no
z_{1ij} = 1 if interview day is Tuesday, 0 if not
z_{2ij} = 1 if interview day is Wed., 0 if not.....
z_{6ij} = 1 if interview day is Sunday, 0 if not
y_{ij} = 1 if sex in last 24 hours, 0 if no

$cor(Y_{ij}, Y_{ij'}) = \rho$ (compound symmetry or exchangeable correlation structure)

Results of Model 3 using STATA

```
. xtgee sx24hrs drgalcoh tues wed thur fri sat sun, eform i(id) family(binomial
> ) cor(exc) robust


GEE population-averaged model                   Number of obs      =      1708
Group variable:                         id      Number of groups   =       109
Link:                                logit      Obs per group: min =         1
Family:                           binomial                     avg =      15.7
Correlation:                  exchangeable                     max =        33
                                                Wald chi2(7)       =     11.40
Scale parameter:                         1      Prob > chi2        =    0.1220

                               (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |             Semi-robust
     sx24hrs | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    drgalcoh |   1.373029   .1845197     2.36   0.018     1.055086    1.786782
        tues |   1.239246   .2320747     1.15   0.252     .8585234    1.788804
         wed |   1.234437   .2523307     1.03   0.303      .826942    1.842734
        thur |   1.099757    .233122     0.45   0.654     .7258761    1.666215
         fri |   .9833647   .1933837    -0.09   0.932     .6688388    1.445799
         sat |   1.277403   .2490991     1.26   0.209     .8716457    1.872043
         sun |   1.577958    .306514     2.35   0.019     1.078331     2.30908
------------------------------------------------------------------------------
```

Model for drug/alcohol use vs. day of week

$$\log it[P(X_{ij}=1 \mid day_{ij})] = \gamma^*{}_0 + \gamma^*{}_1 z_{1ij} + \gamma^*{}_2 z_{2ij} + \cdots + \gamma_6{}^* z_{6ij}$$

X_{ij} = 1 if drug/alcohol use is yes, 0 if no

z_{1ij} = 1 if interview day is Tuesday, 0 if not

z_{2ij} = 1 if interview day is Wed., 0 if not.....

z_{6ij} = 1 if interview day is Sunday, 0 if not

$cor(Y_{ij}, Y_{ij'}) = \rho$ (compound symmetry or exchangeable correlation structure)

Results of drug/alcohol use Model using STATA

```
. xtgee drgalcoh tues wed thur fri sat sun, eform i(id) family(binomial) cor(ex
> c) robust

GEE population-averaged model                   Number of obs      =      1708
Group variable:                         id      Number of groups   =       109
Link:                                logit      Obs per group: min =         1
Family:                           binomial                     avg =      15.7
Correlation:                  exchangeable                     max =        33
                                                Wald chi2(6)       =     28.91
Scale parameter:                         1      Prob > chi2        =    0.0001

                               (standard errors adjusted for clustering on id)
------------------------------------------------------------------------------
             |             Semi-robust
    drgalcoh | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
        tues |   .7484218   .1301296    -1.67   0.096     .5322875    1.052317
         wed |   .7043399   .1440654    -1.71   0.087     .4717131    1.051687
        thur |   .9226514    .171617    -0.43   0.665     .6407825    1.328509
         fri |   1.197263   .2206008     0.98   0.329      .834357    1.718015
         sat |   1.666645   .3147173     2.71   0.007     1.151088    2.413115
         sun |   1.371219    .205994     2.10   0.036     1.021488    1.840688
------------------------------------------------------------------------------
```

Continuous Outcome Example (Linear Model): Respiratory Function

- Random sample of 300 girls from Topeka

- Measurements of fev_1, height, age (fev_1 is forced expired volume in first second after spirometry in ml)

OLS -- ignores correlation (no robust variabilty estimates)

```
. xtgee  lnfev age, family(gaussian) link(id) corr(ind) i( childid)
GEE population-averaged model                 Number of obs      =      1994
Group variable:                   childid      Number of groups   =       300
Link:                            identity      Obs per group: min =         1
Family:                          Gaussian                     avg =       6.6
Correlation:                  independent                     max =        12
                                               Wald chi2(1)       =   6299.69
Scale parameter:                 .0262556      Prob > chi2        =    0.0000

Pearson chi2(1994):                 52.35      Deviance           =     52.35
Dispersion (Pearson):            .0262556      Dispersion         =  .0262556

------------------------------------------------------------------------------
   lnfev |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------------------------------------------------------------
     age |   .0866927   .0010923    79.37   0.000      .084552    .0888335
   _cons |  -.2741518   .014197    -19.31   0.000    -.3019775   -.2463261
------------------------------------------------------------------------------
```

(Same as OLS on entire data set)

. regress lnfev age

lnfev	Coef.	Std. Err.	t	P>|t|	[95% Conf. Interval]	
age	.0866927	.0010928	79.33	0.000	.0845496	.0888359
_cons	-.2741518	.0142042	-19.30	0.000	-.3020084	-.2462953

OLS with Robust Variability Estimates

```
. xtgee  lnfev age, family(gaussian) link(id) corr(ind) i( childid) ro

GEE population-averaged model              Number of obs      =     1994
Group variable:              childid      Number of groups   =      300
Link:                       identity      Obs per group: min =        1
Family:                     Gaussian                     avg =      6.6
Correlation:             independent                     max =       12

                    (standard errors adjusted for clustering on childid)
------------------------------------------------------------------------------
             |             Semi-robust
       lnfev |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------------------------------------------------------------
         age |   .0866927   .0011288    76.80   0.000     .0844804    .0889051
       _cons |  -.2741518   .0158196   -17.33   0.000    -.3051577   -.2431459
------------------------------------------------------------------------------
```

.0011288 as compared to non-robust .0010923 (and .0158 vs .0142)

Review of Modeling Longitudinal vs. X-sectional Associations

- Consider the model:

$$E[Y_{ij} \mid X_{i1} = x_{i1}, X_{ij} = x_{ij}] =$$

$$\beta_0 + \beta_C x_{i1} + \beta_L (x_{ij} - x_{i1})$$

- β_L represents the expected change in Y given a change in X_{ij} relative to the baseline value (X_{i1}) - <u>longitudinal effect</u>.

- β_C represents the expected difference in average Y across two sub-populations that differ by their baseline values, X_{i1} - <u>cross-sectional effect.</u>

Alternative Parameterization

- An identical fit to the data would be:

$$E[Y_{ij} \mid X_{i1} = x_{i1}, X_{ij} = x_{ij}] =$$

$$\beta_0 + \beta_C^* x_{i1} + \beta_L x_{ij}$$

- β_L still represents the expected change in Y given a change in X_{ij} relative to the baseline value (X_{i1}) - <u>longitudinal effect</u>.

- β^*_C represents the difference in the x-sectional vs. longitudinal (or $\beta^*_C = \beta_C - \beta_L$).

Model for Lung Function

- Consider the model:

$$E[Y_{ij} \mid X_{i11} = x_{i11}, X_{ij1} = x_{ij1}, X_{i12} = x_{i12}, X_{ij2} = x_{ij2}] =$$

$$\beta_0 + \beta_1 x_{i11} + \beta_2 x_{ij1} + \beta_3 x_{i12} + \beta_3 x_{ij2}$$

with X_{ij1} height for subject i, time j, and X_{ij2} is the corresponding age.

More complicated Model -- still OLS

xtgee lnfev lnheight age initlnheight initage, family(gaussian) link(id) corr(ind) i(childid)

```
GEE population-averaged model              Number of obs      =     1994
Group variable:               childid      Number of groups   =      300
Link:                        identity      Obs per group: min =        1
Family:                      Gaussian                     avg =      6.6
Correlation:              independent                     max =       12
                                           Wald chi2(4)       = 14199.25
Scale parameter:             .0134473      Prob > chi2        =   0.0000

------------------------------------------------------------------------------
       lnfev |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
------------------------------------------------------------------------------
    lnheight |   2.056183   .0699129    29.41   0.000     1.919156     2.19321
         age |   .0284979   .0021109    13.50   0.000     .0243606    .0326352
initlnheight |   .4074967   .0839699     4.85   0.000     .2429187    .5720746
     initage |   -.016087   .0040224    -4.00   0.000    -.0239708   -.0082032
       _cons |  -.3309375     .02105   -15.72   0.000    -.3721947   -.2896803
------------------------------------------------------------------------------
```

More complicated Model, different parameterization

```
 xtgee  lnfev  lnheightchange agechange initlnheight initage, family(gaussian) link(id) corr(ind)
           i(childid)

Iteration 1: tolerance = 1.427e-13

GEE population-averaged model                      Number of obs      =      1994
Group variable:                      childid      Number of groups   =       300
Link:                               identity      Obs per group: min =         1
Family:                             Gaussian                     avg =       6.6
Correlation:                     independent                     max =        12
                                                  Wald chi2(4)       =  14199.25
Scale parameter:                    .0134473      Prob > chi2        =    0.0000

Pearson chi2(1994):                    26.81      Deviance           =     26.81
Dispersion (Pearson):               .0134473      Dispersion         =  .0134473

------------------------------------------------------------------------------
       lnfev |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
lnheightchange   2.056183   .0699129    29.41   0.000     1.919156     2.19321
   agechange |   .0284979   .0021109    13.50   0.000     .0243606    .0326352
initlnheight |    2.46368   .0649965    37.90   0.000     2.336289    2.591071
     initage |   .0124109    .003436     3.61   0.000     .0056765    .0191453
       _cons |  -.3309375     .02105   -15.72   0.000    -.3721947   -.2896803
------------------------------------------------------------------------------
```

More complicated Model -- still OLS + Robust

xtgee lnfev lnheight age initlnheight initage, family(gaussian) link(id) corr(ind) i(childid) ro

GEE population-averaged model			Number of obs	=	1994
Group variable:	childid		Number of groups	=	300
Link:	identity		Obs per group: min	=	1
Family:	Gaussian		avg	=	6.6
Correlation:	independent		max	=	12

(standard errors adjusted for clustering on childid)

lnfev	Coef.	Semi-robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
lnheight	2.056183	.0792847	25.93	0.000	1.900788	2.211578
age	.0284979	.0022755	12.52	0.000	.024038	.0329578
initlnheight	.4074967	.1828943	2.23	0.026	.0490305	.7659628
initage	-.016087	.008835	-1.82	0.069	-.0334034	.0012293
_cons	-.3309375	.0432665	-7.65	0.000	-.4157383	-.2461367

More complicated Model, different parameterization

```
 . xtgee  lnfev  lnheightchange agechange initlnheight initage, family(gaussian) link(id) corr(ind)
i( childid) ro

Iteration 1: tolerance = 1.427e-13

GEE population-averaged model                   Number of obs      =      1994
Group variable:                    childid      Number of groups   =       300
Link:                             identity      Obs per group: min =         1
Family:                           Gaussian                     avg =       6.6
Correlation:                   independent                     max =        12
                                                Wald chi2(4)       =  11417.58
Scale parameter:                  .0134473      Prob > chi2        =    0.0000

Pearson chi2(1994):                  26.81      Deviance           =     26.81
Dispersion (Pearson):             .0134473      Dispersion         =  .0134473

                          (standard errors adjusted for clustering on childid)
------------------------------------------------------------------------------
             |             Semi-robust
       lnfev |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
lnheightch~e |   2.056183   .0792847    25.93   0.000     1.900788    2.211578
   agechange |   .0284979   .0022755    12.52   0.000      .024038    .0329578
initlnheight |    2.46368   .1775394    13.88   0.000     2.115709    2.811651
     initage |   .0124109   .0087532     1.42   0.156    -.0047451    .0295668
       _cons |  -.3309375   .0432665    -7.65   0.000    -.4157383   -.2461367
------------------------------------------------------------------------------
```

Comparison of Standard Errors

Variable	Naïve SE	Robust SE	Naïve z	Robust z
lnheight	.0699	.0793	29.4	25.9
age	.0021	.0023	13.5	12.5
initlnheight	.0840	.1829	4.8	2.2
initage	.0040	.0088	-4.0	-1.8
_cons	.0211	.0433	-15.7	-7.6