



Biostatistics 140.754  
Advanced Methods in Biostatistics IV

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Lecture 7

## Tip + Paper

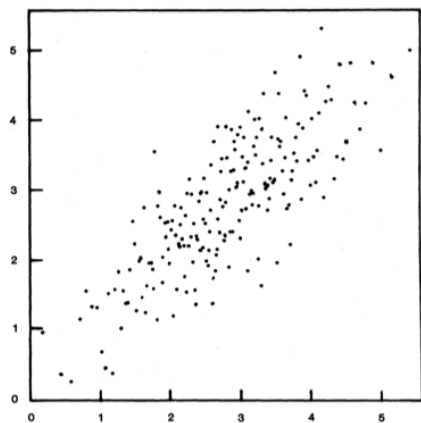
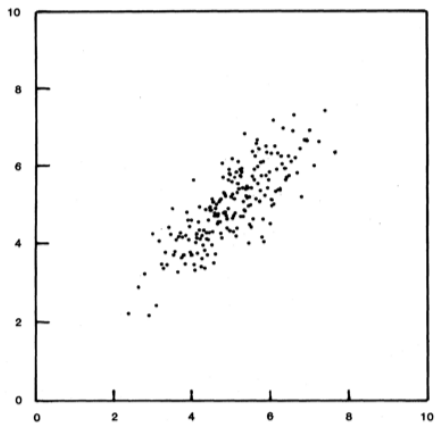
**Tip** When performing exploratory data analysis you will often have the choice of performing a statistical test/summary or making a plot. Make the plot. This doesn't mean don't think! Choosing how to make plots and using them to convince yourself/others that trends are real is an important skill.

### **Paper of the Day:**

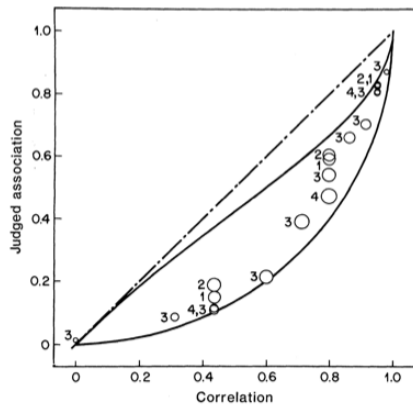
“Variables on scatterplots look more highly correlated when the scales are increased”

<http://www.biostat.jhsph.edu/~jleek/teaching/2011/754/reading/cdm.pdf>

# CDM - Figure 1



# CDM - Figure 2



# Outline For Today

- ▶ GEE!

# Generalized Estimating Equations†

We move to semiparametric inference for vector outcomes, and in particular, **Generalized Estimating Equations**

- ▶ Liang and Zeger (1986) developed GEE as a generalization of earlier quasi-likelihood techniques. GEE and QL have similar robustness properties
- ▶ We will make assumptions about the (true) mean model, and working assumptions about the covariance of the outcomes (notably within-cluster correlations)
- ▶ Familiar sandwich forms are used to provide estimates of the standard error

In many fields, GEE is the “industry standard” method for clustered data, notably longitudinal data. any serious statistical software will implement it.

## GEE: mean model†

In addition to the between-cluster independence seen before, in a GEE “model” we assume a marginal mean model:

$$\mathbb{E}[Y_{ij}|X_{ij}] = g(X_{ij}^T \beta) \equiv \mu_{ij}, \quad \forall i, j$$

-with the usual  $g(\cdot)$  link function

- ▶ “Marginal” means that we condition on  $X_{ij}$  **and nothing else**
- ▶ This is a notable restriction; “transition” models condition on “earlier”  $Y_{ij}$ ; “latent variable” models condition on cluster-specific additional covariates  $b_i$ .  $X_{ij}$  may also matter
- ▶ If  $X_{ij}$  is the same for all  $j$  (e.g. treatment/placebo in a longitudinal clinical trial) or are fixed by design without regard to the other  $\{Y_{ik}, j \neq k\}$ , this conditioning does not reflect the true  $F$ ; but we are still assuming  $g(\cdot)$  is the right link function

Time-varying covariates (based on interim  $Y_{ij}$ ) are not covered here.

## GEE: mean model†

We are conditioning on the observed  $\{X_{ij}\}$ , i.e. frequentist inference considers replications where the covariates are those seen at the observed values <sup>1</sup>

- ▶ Similarly, statements about e.g.  $\text{Cov}[\hat{\beta}]$  will now use  $\text{Cov}[\hat{\beta}|X = x]$ , i.e. we consider running the universe over and over, but using the same  $X$  values observed in our study.
- ▶ Describing the parameter is simpler than for nonparametrics;  $\beta_k$  is the difference/fold-change/odds-ratio in  $\mathbb{E}[Y]$  per one-unit difference in covariate  $k$ , among observations with covariates that are otherwise identical <sup>2</sup>.
- ▶ This is a **stronger** statement than just a “trend”

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<sup>1</sup>... though inferential properties carry over to replications where  $\{X_{ij}\}$  is random.

<sup>2</sup>a.k.a. “keeping everything else fixed”, although this phrase can mislead” ≡



## GEE: mean model†

It's very important to state that we are fitting a **marginal** mean model

- ▶ In general, this statement is an average over non-identical clusters (due to e.g. unmeasured variables)
- ▶ A marginal model *can* result from “integrating out” latent cluster-specific effects (recall non-collapsibility). Mean model parameters between  $Y$  and  $X$  need not be the same in these cases -which do you want?
- ▶ The assumed marginal mean model can be wrong (e.g. non-additivity, non-linearity on the specified scale) or unhelpful (e.g. linear in  $X$  but more interestingly linear in  $X$  at different levels of  $Z$ ). We will discuss model-checking, later.

## GEE: working assumptions†

The estimating equations in GEE generalize what we saw before:

$$\sum_{i=1}^n \frac{\partial g(X_i^T \beta)}{\partial \beta^T} \mathbf{V}_i^{-1} (Y_i - g(X_i^T \beta)) = \mathbf{0}_p$$

To evaluate these, we must specify some choice of  $\{\mathbf{V}_i\}$ . The standard choice of variance is that

$$(\mathbf{V}_i)_{jj} = \phi \mathbf{S}(\mu_{ij})$$

i.e. that the variance of every  $Y_{ij}$  is some specified form  $\mathbf{S}(\cdot)$  of the mean, multiplied by dispersion parameter  $\phi$ .

To complete the working covariance matrix, we require a working choice of the correlation matrix  $\mathbf{R}$  where

$$\mathbf{V}_i = \phi \text{diag}\{\mathbf{S}(\mu_{ij})^{1/2}\} \mathbf{R}_i \text{diag}\{\mathbf{S}(\mu_{ij})^{1/2}\}$$

# GEE: working assumptions†

Some commonly-used correlation structures for  $\mathbf{R}_i$  are:

**Independence:**

$$\mathbf{R}_i = \begin{bmatrix} 1 & 0 & 0 & \cdots & 0 \\ 0 & 1 & 0 & \cdots & 0 \\ 0 & 0 & 1 & \cdots & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ 0 & 0 & 0 & \cdots & 1 \end{bmatrix}$$

**Exchangeable:**

$$\mathbf{R}_i = \begin{bmatrix} 1 & \alpha & \alpha & \cdots & \alpha \\ \alpha & 1 & \alpha & \cdots & \alpha \\ \alpha & \alpha & 1 & \cdots & \alpha \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \alpha & \alpha & \alpha & \cdots & 1 \end{bmatrix}$$

# GEE: working assumptions†

Some commonly-used correlation structures for  $\mathbf{R}_i$  are:

**Auto-regressive (AR1):**

$$\mathbf{R}_i = \begin{bmatrix} 1 & \alpha & \alpha^2 & \cdots & \alpha^{m-1} \\ \alpha & 1 & \alpha & \cdots & \alpha^{m-2} \\ \alpha^2 & \alpha & 1 & \cdots & \alpha^{m-3} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \alpha^{m-1} & \alpha^{m-2} & \alpha^{m-3} & \cdots & 1 \end{bmatrix}$$

**Unstructured:** (symmetric)

$$\mathbf{R}_i = \begin{bmatrix} 1 & \alpha_{12} & \alpha_{13} & \cdots & \alpha_{1m} \\ \alpha_{21} & 1 & \alpha_{23} & \cdots & \alpha_{2m} \\ \alpha_{31} & \alpha_{32} & 1 & \cdots & \alpha_{3m} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \alpha_{m1} & \alpha_{m2} & \alpha_{m3} & \cdots & 1 \end{bmatrix}$$

## GEE: estimating equations†

For now, we assume that  $\phi$  and/or any  $\alpha$  parameters are known. In particular, this lets us evaluate the estimating equations, at any  $\hat{\beta}$ , and consequently to find  $\hat{\beta}$ , the root of the estimating equations.

- ▶ The EEs we used for nonparametric work set (for convenience)  $\mathbf{V}_i = \mathbf{I}_{n_i}$  - actually common in GEE work.
- ▶ We will see that (for correct marginal models)
  - ▶ The resulting  $\hat{\beta}$  is consistent and asymptotically Normal ( $n \rightarrow \infty$ ) under mild regularity conditions (robustness)
  - ▶ We get better  $\hat{\beta}$  when  $\mathbf{V}_i \propto \text{Cov}[Y_i|X_i]$  (efficiency)

## GEE: estimating equations†

For consistency; note that by assumption for any  $\{\mathbf{V}_i^{-1}\}$  we have

$$\mathbb{E}_{X_i} \left[ \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbb{E}_{Y_i|X_i} [Y_i - \mu_i(\boldsymbol{\beta})] \right] = \mathbf{0}_p$$

where  $\mu_i$  denotes the vector of means  $\mathbf{D}_i$  is their matrix of derivatives with respect to  $\boldsymbol{\beta}$ .

Asymptotic Normality of  $\hat{\boldsymbol{\beta}}$  holds because we get it from an average over  $n$  similarly-distributed variables; the usual sandwich  $\mathbf{A}^{-1} \mathbf{B} \mathbf{A}^{-1}$  formula determines the asymptotic variance.

For the  $\mathbf{A}$  matrix, we consider

$$\mathbb{E} \left[ \left( \frac{\partial \mathbf{D}^T}{\partial \boldsymbol{\beta}} \right) \mathbf{V}^{-1} (Y - \mu) + \mathbf{D}^T \left( \frac{\partial \mathbf{V}^{-1}}{\partial \boldsymbol{\beta}} \right) (Y - \mu) - \mathbf{D}^T \mathbf{V}^{-1} \mathbf{D} \right]$$

Using the assumptions of the marginal mean model, only the right hand term here is nonzero. But  $\mathbf{B}$  does not simplify in this way:

$$\mathbf{B} = \mathbb{E}[\mathbf{D}^T \mathbf{V}^{-1} (Y - \mu) (Y - \mu)^T \mathbf{V}^{-1} \mathbf{D}]$$

## GEE: sandwich estimates†

I hope you'd have guessed these (robust) estimates

$$\hat{\mathbf{A}} = (1/n) \sum_{i=1}^n \mathbf{D}_i^T \mathbf{V}_i^{-1} \mathbf{D}_i$$

$$\hat{\mathbf{B}} = (1/n) \sum_{i=1}^n \mathbf{D}_i^T \mathbf{V}_i^{-1} (Y_i - \mu_i) (Y_i - \mu_i)^T \mathbf{V}_i^{-1} \mathbf{D}_i$$

where everything is evaluated at the point estimates for all relevant parameters, and for inference we use

$$\widehat{\text{Cov}}[\hat{\beta}] = \hat{\mathbf{A}}^{-1} \hat{\mathbf{B}} \hat{\mathbf{A}}^{-1} / n$$

... some authors/code use summation (not averages) in  $\hat{\mathbf{A}}, \hat{\mathbf{B}}$  which removes the  $1/n$  term in the resulting sandwich estimate.

Asymptotically-justified confidence intervals result, in the usual way, without further assumptions. Wald tests of e.g.,  $H_0 : \beta_j = 0$  also use familiar machinery.

## Example: measles data†

Sherman and Le Cessie (1997, on the class site) studied number of cases of measles in preschool children, in 15 counties in the US, between 1985 and 1991.

For each county the annual number of preschoolers with measles was recorded, as well as factors possibly related to measles incidence, like immunization rate, and density of preschoolers per county.

The data are annual for each county. We know:

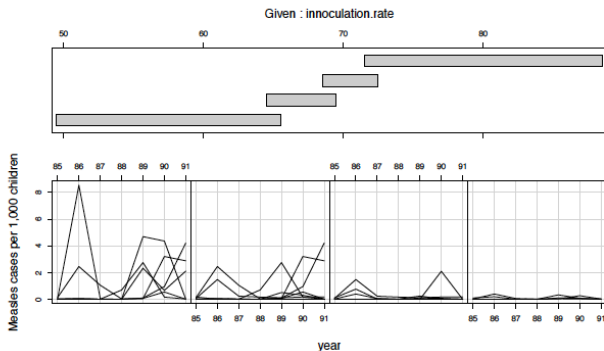
- ▶ Number of cases of measles
- ▶ Immunization rate (percentage, fixed over time)
- ▶ Total number of preschoolers

We want to know the association between immunization rate and measles incidence.



## Example: measles data†

The measles data via coplot; what trend do you notice?



## Example: measles data†

For number of measles cases  $y_{ij}$  and immunization rate  $x_{ij} = x_i$  to fit a line of the form

$$y_{ij} = \text{n.children}_{ij} \times e^{\beta_0 + \beta_1 x_{ij}}$$

... it's sane to use these estimating equations:

$$\sum_{i=1}^n X_i (Y_i - \mu_i) = \mathbf{0}_2$$

where  $\mu_{ij} = \exp(\log(\text{n.children}_{ij}) + \beta_0 + \beta_1 X_{ij})$

The term  $\log(\text{n.children}_{ij})$  is called an offset, think of it as a covariate whose coefficient is fixed to be 1, regardless of the other data.

Similarly to the previous example, we can solve these EEs using `glm()`; the solution is  $\hat{\beta} = \{-0.458, -0.108\}$ .

## Example: measles data†

For the measles data, we could assume:

$$\mathbb{E}[Y_{ij}|X_{ij} = x_{ij}] = \text{n.children}_{ij} \times e^{\beta_0 + \beta_1 x_{ij}}$$

Now, we are making a semi-parametric assumption; comparing observations where  $x_{ij}$  differs by  $\Delta(x)$ , the expected rates of measles cases differ by a factor of  $\exp(\beta_1)\Delta(x)$ , for any  $\Delta(x)$ . In particular, the expected rate of measles cases differs by  $\exp(\beta_1)$  for each one-unit difference in  $x_{ij}$ .

The estimating equations are exactly those we saw on the previous page.

## Example: measles data†

Coding this is slightly simpler than the non-parameteric version; there is no need to work out second derivatives in  $\hat{\mathbf{A}}$ .

```
measles <- read.table("measlesdata.txt",header=T)
measles$county <- as.character(measles$county)

# Same helper function as before
sum.list <- function(l1){
  l <- length(l1); out <- l1[[1]]
  for(i in 2:l){out <- out + l1[[i]]}
  out}

glm1 <- glm(cases ~ rate + offset(log(children)), data=measles, family=poisson)
measles$muhat <- fitted(glm1)
# i.e. hte point estimates - these include the offset

allAi <- by(measles, measles$county, simplify=F,function(data){ ni <- dim(data)[1]
Xi <- cbind(rep(1,ni),data$rate)
Di <- Xi * data$muhat
Vi <- diag(data$muhat)
# could use crossprod t(Di)%*% solve(Vi) %*%Di
})

Ahat <- sum.list(allAi)
```

## Example: measles data†

We can similarly code  $\hat{\mathbf{B}}$ , and get the sandwich estimate

```
allBi <- by(measles, measles$county, simplify=F, function(data) {  
  ni <- dim(data)[1]  
  Xi <- cbind(rep(1, ni), data$rate)  
  Di <- Xi * data$muhat  
  Vi <- diag(data$muhat)  
  resid <- data$cases - data$muhat  
  t(Di) %*% solve(Vi) %*% resid %*% t(resid) %*% solve(Vi) %*% Di  
})  
Bhat <- sum.list(allBi)
```

```
sand1 <- solve(Ahat) %*% Bhat %*% solve(Ahat)
```

- ▶ Where did  $\phi$  go? (Hint: count the  $\mathbf{V}$  terms in the formulae)
- ▶ Within each cluster, these calculations should be familiar from the univariate case
- ▶ `crossprod()` is faster, `sum.list()` is clunky
- ▶ Premature optimization is the root of all evil (Donald Knuth)

## Example: measles data†

Finally the answers:

```
> coeff(glm1)
(Intercept)  rate
-0.4581488 -0.1081273
> sqrt(diag(sand1))
[1] 1.01237231  0.01589211
> coeff(glm1) + sqrt(diag(sand)) %o% qnorm(c(0.25,0.975))
[,1] [,2]
[1,] -2.4423621  1.52606448
[2,] -0.1392755  -0.07697913
```

- ▶ Comparing measles incidence where the rate differs by one percentage point, the estimated log-rate ratio is -0.11 (-0.14, -0.08). The estimates RR is 0.90 (0.87, 0.93)
- ▶ A naïve standard error, assuming independence, estimates the standard error to be 0.002 (Poisson model-based) or 0.021 (robust)

## Example: measles data†

A non-trivial factor in the success of GEE is the availability of (free) software that implements it, at little hassle to the user.

We consider the `gee` package (Carey, Lumley, and Ripley). The syntax is similar to that of `glm()`, but an `id` must be specified, indicating cluster membership.

```
> library(gee) > gee1 <- gee(cases ~ rate + offset(log(children)),data=measles,id=county,
family = "poisson", corstr="independence")
Beginning Cgee S-function (#) geeformula.q.4.13 98/01/27
running glm to get initial regression estimate
(Intercept) rate
-0.458149 -0.108127
```

Similar to our implementation, output from `glm()` is used for parts of the calculation.

## Example: measles data†

```
> summary(gee1) GEE: GENERALIZED LINEAR MODELS FOR DEPENDENT DATA
gee S-function, version 4.13 modified 98/01/27 (1998)
Model:
Link: Logarithm
Variance to Mean Relation: Poisson
Correlation Structure: Independent
Coefficients:
Estimate Naive S.E. Naive z Robust S.E. Robust z
(Intercept) -0.458149 1.5370065 -0.298079 1.0123723 -0.45255
rate -0.108127 0.0240767 -4.490956 0.0158922 -6.80379
Estimated Scale Parameter: 155.89
Number of Iterations: 1 # nothing to update, for corstr=indep't

> sqrt(diag(gee1$robust.variance))
(Intercept) rate
1.0123723 0.0158922
> mean(((fitted(glm1) - measles$cases)^2/fitted(glm1))*105/(105-2))

[1] 155.89
```

The scale parameter  $\phi$  is the standard bias-corrected Pearson estimator (see QL notes).



- ▶ A wide range of family options are supported
- ▶ Do read the documentation, in particular that “data are assumed to be sorted so that observations on a cluster are contiguous rows for all entities in the formula”. This means that `id = c(1,1,0,0,1,1,0,0)` gets you four clusters, each with two observations.
- ▶ Observations with relevant missing values are omitted. See earlier discussion on informative cluster size- but also watch out if using `gee()` for several regressions, that have different covariates.
- ▶ Get rid of the irritating Cgee message by making a copy of the `gee()` function, and removing its `message()` call.

Also be aware of `geepack`, which features a `glmgee()` function.

- ▶ Has the same syntax as `gee()`
- ▶ It calls function `geese()`, which in turn calls `geese.fit()`
- ▶ Slightly different internal calculations, e.g. dispersion parameters, sandwich estimate, which are not (quite) those given here
- ▶ Output is designed to mimic that of `glm()`, which is good if you are intricately familiar with that setup
- ▶ Permits use of `anova()` .. should you want that
- ▶ Messes around with `options('digits')`, on some machines
- ▶ Can crash R (!) - see documentation

## GEE: working correlation†

The inverse-weighting matrix  $\mathbf{V}_i$  is known as the “working” covariance matrix. This terminology emphasizes that exact knowledge of the true covariance is not required; we get consistency, asymptotic Normality and valid sandwich-based intervals regardless of the choice.

(If we additionally assume a variance structure, further simplification occurs in the sandwich - that is what our presentation of QL did for the univariate case. But this is not standard GEE practice; robustness to variance assumptions is attractive)

Following the same principles as Aitken/Gauss-Markov/Godambe and Heyde, to get efficiency we should choose each “working”  $\mathbf{V}_i$  to be as close as possible to proportional to the true variance-covariance matrix of elements in each  $Y_i$ .

How much difference does it actually make?

## GEE: choice of working correlation†

Asymptotic relative efficiency, (relative to the “right” choice) for  $n_i = 10$  (Liang and Zeger 1986, Table 1)

Trur Corr'n	$\alpha$	Working correlation		
		Indep	Exch	AR1
Exch	0.3	0.99	1.00	0.95
	0.7	0.99	1.00	0.72
AR	0.3	0.97	0.97	1.00
	0.7	0.88	0.88	1.00

- ▶ Minor correlation  $\implies$  choice doesn't matter
- ▶ Large correlation  $\implies$  large efficiency loss possible

The same caveats apply as with univariate regression; an extra 10% of efficiency may not change practical inference based on very precise/imprecise estimates. The choice of working correlation structure should be based on external information - “picking the best” induces the “wiggle room” problem.

# GEE: choice of working correlation†

Fitzmaurice (1995) showed the answer depends on covariate design (here  $r =$  within-subject correlation,  $T = n_i$ ).

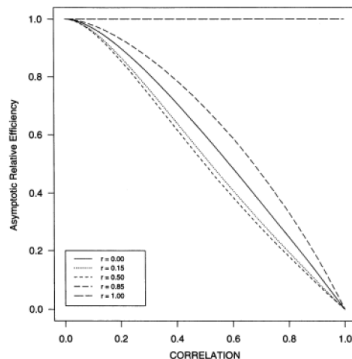
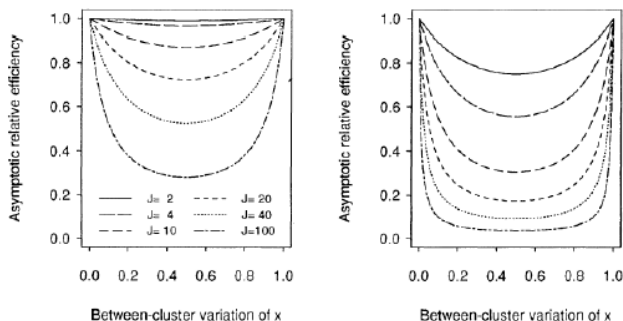


Figure 2. Asymptotic efficiency of the Exchangeable GEE estimator, relative to the Independence estimator, for selected values of the intra-cluster correlation for the covariate (and when  $T = 5$ ).

Large ICC  $\implies$  big efficiency loss

# GEE: choice of working correlation†

Cluster size also matters (Mancl and Leroux 1996)



**Figure 1.** Asymptotic relative efficiency of independence to exchangeable for the case of constant weights, equal cluster sizes ( $J$ ), and common pairwise correlation between responses of (a)  $\rho_y = 0.1$  and (b)  $\rho_y = 0.5$ .

- ▶ Small clusters  $\implies$  possibly minor efficiency loss
- ▶ Large clusters  $\implies$  possibly major efficiency loss

## GEE: estimating $\alpha$ †

Except for independence working correlation assumptions, unknown parameters  $\alpha$  have to be estimated.

However, as with “plug-in” and operations seen earlier, it turns out that <sup>3</sup> any consistent estimator  $\hat{\alpha}$  can be “plugged in” for this unknown, and (in large samples) the behavior of  $\beta$  is the same as if  $\alpha$  were known. Showing this formally will happen in your stat theory class, but the result is not magic. Informally the argument is

- ▶ For known  $\mathbf{R}(\alpha)$ , estimator  $\hat{\beta}_{\alpha}$  is consistent for  $\beta$
- ▶ Estimating  $\alpha$  in any (sane) way will give a  $\hat{\alpha}$  that is consistent for some value  $\alpha'$
- ▶ If  $\hat{\alpha} \rightarrow \alpha'$  sufficiently quickly,  $\hat{\beta}_{\hat{\alpha}}$  is consistent for  $\beta$

Note focusing on consistency alone upsets some people (e.g. Drum and McCullagh) - & in low power settings this is fair.

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<sup>3</sup>basically! ... mild regularity conditions apply

## GEE: estimating $\alpha$ †

The consistency result motivates finding straightforward estimates of  $\alpha$  that we can incorporate into a fitting procedure for both  $\hat{\beta}$  and  $\hat{\alpha}$ .

Liang and Zeger (1986) proposed the following moment based estimators of  $\alpha$ , making use of Pearson residuals:

$$e_{ij} = \frac{Y_{ij} - g(X_{ij}^T \hat{\beta})}{\sqrt{V(g(X_{ij}^T \hat{\beta}))}}$$

Exchangeable

$$\hat{\alpha} = \frac{1}{n} \sum_{i=1}^n \frac{1}{n_i(n_i - 1)} \sum_{j=j'} e_{ij} e_{ij'}$$

i.e. averaging the products of all pairs of residuals where the pairs are formed within clusters.



## GEE: estimating $\alpha$ †

Autoregressive (AR1):

$$\hat{\alpha} = \frac{1}{n} \sum_{i=1}^n \frac{1}{(n_i - 1)} \sum_{j \leq n_i - 1} e_{ij} e_{i,j+1}$$

i.e. averaging the products of all pairs of residuals, where the pairs are “neighbors” within cluster.

Unstructured:

$$\hat{\alpha}_{jj'} = \frac{1}{n} \sum_{i=1}^n e_{ij} e_{ij'}$$

i.e. averaging the products of all pairs of residuals at positions  $j$  and  $j'$ , over all clusters.

.... together with independence, which has no  $\alpha$  to estimate, these working correlation matrices are “built in” to standard GEE software. For others ... roll up your sleeves.

## GEE: fitting algorithm†

The GEE fitting algorithm:

1. Start with initial  $\hat{\beta}^0$ , obtained from e.g. a univariate analysis - typically by using `glm()`
2. (a) Calculate Pearson residuals, (b) calculate  $\hat{\alpha}$ , based on current  $\hat{\beta}$  and  $\{\mu_i\}$
3. Update  $\hat{\beta}$ , by setting:

$$\beta^{(s+1)} = \beta^{(s)} + \left( \sum_{i=1}^n \mathbf{D}_i^T \mathbf{V}_i(\hat{\alpha})^{-1} \mathbf{D}_i \right)^{-1} \left( \sum_{i=1}^n \mathbf{D}_i^T \mathbf{V}_i(\hat{\alpha})^{-1} (Y_i - \mu_i) \right)$$

Repeat 2 and 3 until convergence. This algorithm generalizes the Fisher scoring method you saw earlier. It is one (good) way to solve simultaneously for  $\hat{\alpha}$  and  $\hat{\beta}$ .

## GEE: Dental growth example†

Recall the dental growth data from earlier; we have  $n = 27$  clusters (children), with measurements at  $n_i = 4$  time points (8, 10, 12, 14 years old).

Coding the covariates as:

$$X_{ij} = \{1, (\text{Age}_{ij} - 8), \text{Male}_{ij}, (\text{Age}_{ij} - 8) \times \text{Male}_{ij}\}$$

(a little redundantly in some cases!) we fit the mean model:

$$\mathbb{E}[Y_{ij}|X_{ij}] = \beta_0 + \beta_1(\text{Age}_{ij} - 8) + \beta_2\text{Male}_{ij} + \beta_3(\text{Age}_{ij} - 8) \times \text{Male}_{ij}$$

We will use no mean-variance relationship to weight the EEs, i.e.

$\mathbf{S}(\mu) = 1$ , or equivalently

$$\mathbf{V}_i = \phi \mathbf{R}_i$$

# GEE: Dental growth example†

After carefully setting up the data so contiguous rows represent contiguous observations within a cluster;

```
dental <- read.table("growth.txt")
d3 <- reshape(dental, varying=2:5, direction="long")
names(d3) <- c("id","male","age","distance")
d4 <- d3[ order(d3$id, d3$age), ] # order by id, then age
```

... we investigate different choices of **R**;

```
library("gee") gee1 <- gee(distance I(age-8)*male, id=id, data=d4, corstr="independence")
gee2 <- gee(distance I(age-8)*male, id=id, data=d4, corstr="exchangeable")
gee3 <- gee(distance I(age-8)*male, id=id, data=d4, corstr="AR-M", Mv=1)
gee4 <- gee(distance I(age-8)*male, id=id, data=d4, corstr="unstructured")
```

# GEE: Dental growth example†

## The results

	$\hat{\beta}_0$ (SE)	$\hat{\beta}_1$ (SE)	$\hat{\beta}_2$ (SE)	$\hat{\beta}_3$ (SE)
1. Indept	21.2 (0.56)	0.48 (0.06)	1.41 (0.77)	0.30 (0.12)
2. Exchg	21.2 (0.56)	0.48 (0.06)	1.41 (0.77)	0.30 (0.12)
3. AR1	21.2 (0.59)	0.48 (0.06)	1.56 (0.82)	0.29 (0.12)
4. Unstr	21.2 (0.55)	0.48 (0.06)	1.41 (0.76)	0.31 (0.12)
Naïve <code>lm()</code>	21.2 (0.50)	0.48 (0.15)	1.41 (0.70)	0.30 (0.19)

- ▶ Independence and `lm()` give same estimates - as seen before
- ▶ Here, Independence and Exchangeable give identical results (balanced design, complete data - think of it as just a coincidence)
- ▶ Inference involving  $\hat{\beta}_2$  is sensitive - but not badly
- ▶ Naïve approach SEs for Age effects are noticeably off (and wrong)

## GEE: Dental growth example†

The working.correlation from each gee.object

$$\begin{aligned} 2. \text{ Exchangeable } \mathbf{R}_i(\hat{\alpha}) &= \begin{bmatrix} 1.00 & 0.61 & 0.61 & 0.61 \\ & 1.00 & 0.61 & 0.61 \\ & & 1.00 & 0.61 \\ & & & 1.00 \end{bmatrix} \\ 3. \text{ AR-1 } \mathbf{R}_i(\hat{\alpha}) &= \begin{bmatrix} 1.00 & 0.61 & 0.38 & 0.23 \\ & 1.00 & 0.61 & 0.38 \\ & & 1.00 & 0.61 \\ & & & 1.00 \end{bmatrix} \\ 4. \text{ Unstructured } \mathbf{R}_i(\hat{\alpha}) &= \begin{bmatrix} 1.00 & 0.50 & 0.74 & 0.51 \\ & 1.00 & 0.56 & 0.62 \\ & & 1.00 & 0.78 \\ & & & 1.00 \end{bmatrix} \end{aligned}$$

# GEE: Dental growth example†

Key bits of the output, with Independence Working Correlation

	Estimate	Naive S.E.	Naive z	Robust S.E.	Robust z
(Intercept)	21.2090909	0.5693435	37.251833	0.5604314	37.844221
I(age - 8)	0.4795455	0.1521635	3.151515	0.0631326	7.595845
male	1.4065341	0.7395990	1.901752	0.7737993	1.817699
I(age - 8):male	0.3048295	0.1976661	1.542143	0.1168673	2.608339
Estimated Scale Parameter:		5.093818			

- ▶ Naïve SE is the model-based variety, with no clustering
- ▶ Default is the robust SEs, i.e. use of the sandwich. This is what you should use
- ▶ Scale parameter  $\equiv \phi$  - not required, but useful for thinking about model-checking, and/or coding snafus. Also, for e.g. roughly-Poisson data, you may want to know how far “off” you are.

## GEE: Dental growth example†

Key bits of the output, with AR-1 working correlation

Coefficients:

	Estimate	Naive S.E.	Naive z	Robust S.E.	Robust z
(Intercept)	21.1914047	0.6691392	31.669651	0.58665343	36.122528
I(age - 8)	0.4837647	0.1406311	3.439956	0.06291492	7.689189
male	1.5588576	0.8692373	1.793363	0.81581249	1.910804
I(age - 8):male	0.2856922	0.1826851	1.563850	0.12238030	2.334462
Estimated Scale Parameter:	5.099523				

- ▶ Naïve SE is the model-based variety, with no clustering, and weighting determined by  $\mathbf{R}(\hat{\alpha})$  - i.e. an example of WLS. If the full variance specification is right, these are valid.
- ▶ Sandwich is robust; recall our *working* covariance assumptions
- ▶ Use any difference to (informally) guide any discussion of what is wrong, in the model-based inference



## GEE: choice of correlation structure†

Does choice of  $\mathbf{R}$  matter? It depends who you ask...

- ▶ Liang and Zeger (1986): ... *little difference when correlation is moderate*
- ▶ McDonald (1993): The independence estimator *may be recommended for practical purposes*
- ▶ Zhao, Prentice, and Self (1992): assuming independence *can lead to important losses of efficiency*
- ▶ Fitzmaurice, Laird, and Rotnitzky (1993): ... *important to obtain a close approximation to  $\text{Cov}[Y_i]$  in order to achieve high efficiency*

... in fairness, they'd also all tell you it depends on the applied problem.

Whether or not efficiency matters will depend on how much precision you (plausibly) have. Working that out is context-specific; what  $\{\mathbf{R}, n\boldsymbol{\beta}, \phi\}$  are realistic?

## GEE: model checking†

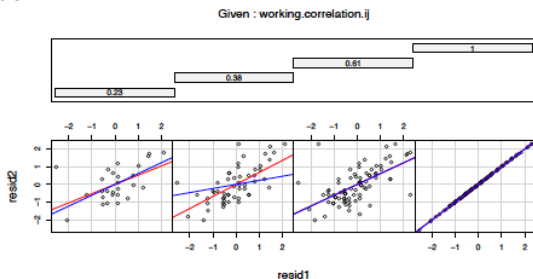
The diagnostics we used in Chapter 1 can be used with GEE (and other methods for vector outcomes);

- ▶ Plot (and smooth) residuals against fitted values, or against covariates: to identify deviations from your mean model and/or to check that the fitted model is a sane summary of the data
- ▶ Plot (and smooth) Pearson residuals against fitted values, or against covariates: to check that the true variance structure is not egregiously far from your working variance assumptions - using sandwich methods, the concern here is efficiency.
- ▶ Leave one cluster out: to flag up problems with asymptotics,  $DFBETA_i$  can be helpful.

Keep diagnostics in perspective, GEE only requires that the mean model be correct.

# GEE: model checking†

Evaluating the correlation structure is trickier. We can scatterplot pairs of residuals  $\{R_{ij}, R_{ij'}\}$ , conditional on how correlated they “should” be.



Blue/red lines indicated fitted correlation/empirical correlation.  
Axes are picked arbitrarily, here - so pairs only appear once.

## GEE: model checking†

Practical power for model-checking is often very limited.  
Hence, pragmatically

*When regression coefficients are the scientific focus, as in the examples here, one should invest the lion's share of time in modeling the mean structure, while using a reasonable approximation to the covariance. The robustness of the inference about  $\beta$  can be checked by fitting a final model using different covariance assumptions and comparing the two sets of estimates and their robust standard errors. If they differ substantially, a more careful treatment of the covariance model may be necessary.*

-DHLZ 7.5

## GEE: summary†

- ▶ Treating clusters as outcomes, we get inference on marginal parameters
- ▶ GEE inference with sane mean models is robust and reasonably well-calibrated. Obtaining reasonable efficiency requires some thought but is not impossible.
- ▶ GEE is a standard tool: “clustering by id” and “working correlation matrix” are concepts non-statisticians have learned to use (expect to help them describe marginal parameters)
- ▶ GEE does not answer every question you could ask.