Generalized Marginal Models for Longitudinal Data (Inference and Analysis)

Recall...

We specified a **generalized linear marginal model (GLMM)** by using a **link function** which connects the **conditional mean** to a **linear predictor**, alongside a **variance function** which depends on the mean, and **pairwise association** matrix.

That is, 
$$g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$$
 with  $var(Y_{ij}) = \phi V(\mu_{ij})$  and  $cor(Y_{ij}, Y_{i\ell}) = \mathbf{R}_i(\rho)$ .

How do we estimate these models?

Further recall...

That if  $U(\theta, \mathbf{Y}) = \frac{1}{n} \sum_{i=1}^{n} \Psi_i(Y_i, \theta)$ , with  $U(\widehat{\theta}, \mathbf{Y}) = 0$ , then  $\widehat{\theta}$  is consistent (and asymptotically normal) for  $\theta_0$  where  $\theta_0$  is such that  $E[U(\theta_0, \mathbf{Y})] = 0$ .

This is an M-estimator and it carries with it nice properties!

What if **we** formed an **M-estimator** based on our assumptions from the **GLMM**?

• We have specified that  $g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$ .

- We have specified that  $g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$ .
- ▶ This is equivalently,  $\mu_{ij} = E[Y_{ij}|X_{ij}] = g^{-1}(X_{ij}\beta)$ .

- We have specified that  $g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$ .
- ▶ This is equivalently,  $\mu_{ij} = E[Y_{ij}|X_{ij}] = g^{-1}(X_{ij}\beta)$ .
- ▶ Define  $\Psi_{ij}(Y_{ij}, X_{ij}, \beta) = Y_{ij} g^{-1}(X_{ij}\beta)$ .

- We have specified that  $g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$ .
- ▶ This is equivalently,  $\mu_{ij} = E[Y_{ij}|X_{ij}] = g^{-1}(X_{ij}\beta)$ .
- ▶ This is such that  $E[\Psi_{ij}(Y_{ij}, X_{ij}, \beta)] = 0$  at the **true**  $\beta$ .

- We have specified that  $g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$ .
- ▶ This is equivalently,  $\mu_{ij} = E[Y_{ij}|X_{ij}] = g^{-1}(X_{ij}\beta)$ .
- ▶ This is such that  $E[\Psi_{ij}(Y_{ij}, X_{ij}, \beta)] = 0$  at the **true**  $\beta$ .
- This suggests using

$$\sum_{i=1}^n \left\{ Y_{ij} - g^{-1}(X_{ij}\beta) \right\}.$$

- We have specified that  $g(E[Y_{ij}|X_{ij}]) = X_{ij}\beta$ .
- ▶ This is equivalently,  $\mu_{ij} = E[Y_{ij}|X_{ij}] = g^{-1}(X_{ij}\beta)$ .
- ▶ This is such that  $E[\Psi_{ij}(Y_{ij}, X_{ij}, \beta)] = 0$  at the **true**  $\beta$ .
- This suggests using

$$\sum_{i=1}^n \left\{ Y_{ij} - g^{-1}(X_{ij}\beta) \right\}.$$

We could equivalently do this as

$$\sum_{i=1}^n \left\{ Y_i - g^{-1}(X_i\beta) \right\}.$$

► This approach *would* work!

- ► This approach would work!
- ▶ This is not going to be the **most efficient** estimator.

- ► This approach would work!
- ▶ This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

- ► This approach would work!
- ▶ This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

Here,

- ► This approach would work!
- ▶ This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

- Here,
  - $ightharpoonup D_i = rac{\partial}{\partial eta} g^{-1}(X_i eta)$  (a  $k \times p$  matrix).

- ► This approach would work!
- ▶ This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

- Here,

  - $V_i = \phi A_i^{1/2} \mathbf{R}_i(\rho) A_i^{1/2}$  is the working covariance matrix  $(k \times k)$ .

- This approach would work!
- ▶ This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

- Here,

  - $V_i = \phi A_i^{1/2} \mathbf{R}_i(\rho) A_i^{1/2}$  is the working covariance matrix  $(k \times k)$ .
  - ▶  $V_i$  will generally be a function of  $\mu_i = g^{-1}(X_i\beta)$ .

- This approach would work!
- ▶ This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

- Here,

  - $V_i = \phi A_i^{1/2} \mathbf{R}_i(\rho) A_i^{1/2}$  is the working covariance matrix  $(k \times k)$ .
  - ▶  $V_i$  will generally be a function of  $\mu_i = g^{-1}(X_i\beta)$ .
- Note, this is essentially just QMLE!

- This approach would work!
- ► This is not going to be the **most efficient** estimator.
- ▶ We turn to **Generalized Estimating Equations** (GEE), which define

$$U(\beta) = \sum_{i=1}^{n} D'_{i} V_{i}^{-1} (Y_{i} - g^{-1}(X_{i}\beta)).$$

- Here,

  - $V_i = \phi A_i^{1/2} \mathbf{R}_i(\rho) A_i^{1/2}$  is the working covariance matrix  $(k \times k)$ .
  - ▶  $V_i$  will generally be a function of  $\mu_i = g^{-1}(X_i\beta)$ .
- ▶ Note, this is *essentially* just QMLE!
- We will see some specific examples in the next lecture!

# Asymptotic Inference of GEE

From this estimator we get  $\widehat{\beta} \dot{\sim} N(\beta, \text{var}(\widehat{\beta}))$ .  $\text{var}(\widehat{\beta}) = J^{-1} \Gamma J^{-1'}$ , as we saw for **M-estimators** generally.

$$J = E\left[-\frac{\partial}{\partial \beta}U(\beta)\right] = \sum_{i=1}^{n} D_{i}'V_{i}^{-1}D_{i}$$

$$\Gamma = E\left[U(\beta)U(\beta)'\right] = \sum_{i=1}^{n} D_{i}'V_{i}^{-1} \operatorname{var}(Y_{i})V_{i}^{-1}D_{i}$$

#### Scale Parameters

Typically  $\rho$  and  $\phi$  are considered **nuisance** parameters.

In the **GEE method** they are estimated **ad-hoc** based on formulas from **Pearson** Residuals.

The *specific* formula for  $\widehat{\rho}$  and  $\widehat{\phi}$  are **unimportant**, typically.

$$\widehat{r}_{ij} = \frac{Y_{ij} - \widehat{\mu}_{ij}}{\sqrt{V(\widehat{\mu}_{ij})}}$$

$$\widehat{\phi} = \frac{1}{N - p} \sum_{i=1}^{n} \sum_{j=1}^{k_i} \widehat{r}_{ij}^2$$

$$\widehat{\rho}_{jk} = \frac{1}{\widehat{\phi}(n - p)} \sum_{i=1}^{n} \widehat{r}_{ij} \widehat{r}_{ik}.$$

1. Wald procedures based on asymptotic normality.

- 1. Wald procedures based on asymptotic normality.
- 2. Generalized score statistics, which extends the LRT to GEEs.

- 1. Wald procedures based on asymptotic normality.
- 2. Generalized score statistics, which extends the LRT to GEEs.
  - ► Test  $H_0$  :  $C\beta = 0$ .

- 1. Wald procedures based on asymptotic normality.
- 2. **Generalized score statistics**, which extends the LRT to GEEs.
  - ► Test  $H_0$  :  $C\beta = 0$ .
  - $V(\widetilde{\beta}_G)'\mathbf{G}_mC'[C\mathbf{G}_rC']^{-1}C\mathbf{G}_mU(\widetilde{\beta}_G)\sim \chi_r^2$

- 1. Wald procedures based on asymptotic normality.
- 2. Generalized score statistics, which extends the LRT to GEEs.
  - ► Test  $H_0$ :  $C\beta = 0$ .
  - lacksquare  $U(\widetilde{\beta}_G)'\mathbf{G}_mC'[C\mathbf{G}_rC']^{-1}C\mathbf{G}_mU(\widetilde{\beta}_G)\sim \chi_r^2$
  - $ightharpoonup \widetilde{\beta}_G$  is the GEE estimator assuming  $H_0$ .

- 1. Wald procedures based on asymptotic normality.
- 2. Generalized score statistics, which extends the LRT to GEEs.

  - $V(\widetilde{\beta}_G)'\mathbf{G}_mC'[C\mathbf{G}_rC']^{-1}C\mathbf{G}_mU(\widetilde{\beta}_G)\sim \chi_r^2$
  - $ightharpoonup \widetilde{\beta}_G$  is the GEE estimator assuming  $H_0$ .
  - $ightharpoonup \mathbf{G}_m = \widehat{J}^{-1}$  and  $\mathbf{G}_r = \widehat{J}^{-1}\widehat{\Gamma}\widehat{J}^{-1}$ .

- 1. Wald procedures based on asymptotic normality.
- 2. **Generalized score statistics**, which extends the LRT to GEEs.

  - $U(\widetilde{\beta}_G)' \mathbf{G}_m C' [C\mathbf{G}_r C']^{-1} C\mathbf{G}_m U(\widetilde{\beta}_G) \sim \chi_r^2$
  - $ightharpoonup \widetilde{\beta}_G$  is the GEE estimator assuming  $H_0$ .
  - $ightharpoonup \mathbf{G}_m = \widehat{J}^{-1}$  and  $\mathbf{G}_r = \widehat{J}^{-1}\widehat{\Gamma}\widehat{J}^{-1}$ .
  - You do not need to learn this!

- 1. Wald procedures based on asymptotic normality.
- 2. **Generalized score statistics**, which extends the LRT to GEEs.
  - ► Test  $H_0$ :  $C\beta = 0$ .
  - $U(\widetilde{\beta}_G)'\mathbf{G}_mC'[C\mathbf{G}_rC']^{-1}C\mathbf{G}_mU(\widetilde{\beta}_G) \sim \chi_r^2$
  - $ightharpoonup \widetilde{\beta}_G$  is the GEE estimator assuming  $H_0$ .
  - $ightharpoonup \mathbf{G}_m = \widehat{J}^{-1}$  and  $\mathbf{G}_r = \widehat{J}^{-1}\widehat{\Gamma}\widehat{J}^{-1}$ .
  - ► You do not need to learn this!
- 3. Can also modify AIC to produce QIC.

Inference is **valid** even if  $V_i$  is incorrectly specified. Why do we bother?

#### Parameter Interpretation

# Parameters in **marginal models** are interpreted as **population-level effects**.

That is,  $\beta_j$  is the impact of variate j on average, across the whole population (assuming other variates fixed).

These are **not** individual level effects!

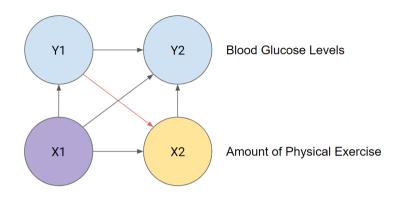
The linear structure of our marginal models **implicitly assumes** that  $Y_{ij} \perp X_{ik} | X_{ij}$ , for all  $j \neq k$ .

That is, the **outcome** is *conditionally* independent of explanatory factors at **all other times**, given the **current time's** explanatory factors.

► This will generally be true of **time invariant** variables.

- ► This will generally be true of **time invariant** variables.
- ▶ This will also generally be true of **deterministic**, **time-varying** variables.

- ► This will generally be true of **time invariant** variables.
- ► This will also generally be true of **deterministic**, **time-varying** variables.
- ► This will not be generally true of **stochastic**, **time-varying** variables.





• We can use **generalized estimating equations** to solve for the  $\beta$  parameters in a marginal model.

- We can use **generalized estimating equations** to solve for the  $\beta$  parameters in a marginal model.
- ► This procedures results in **asymptotically normal** estimators, allowing for standard inference.

- We can use **generalized estimating equations** to solve for the  $\beta$  parameters in a marginal model.
- ➤ This procedures results in **asymptotically normal** estimators, allowing for standard inference.
- ▶ The parameters are **population averaged** effects, *not* individual.

- We can use **generalized estimating equations** to solve for the  $\beta$  parameters in a marginal model.
- ► This procedures results in **asymptotically normal** estimators, allowing for standard inference.
- ▶ The parameters are **population averaged** effects, *not* individual.
- We need to be mindful of stochastic, time-varying covariates.