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Marginalized Multilevel Models

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Introduction

Model for longitudinal and clustered binary data must describe systematic variations in mean responses and account for non-independent observations

1. Generalized linear mixed models (GLMM: Laird and Ware, 1982)

   Accounts for dependence by assuming unobserved random effects. Mean models are constructed conditional on the latent variables.

2. Marginal models with generalized estimating equations (GEE) (Liang and Zeger, 1986)

   Specifies separate regression models for first and second moments: marginal means and association model

More on GLMM

Model:

$$\text{logit}E\left(Y_{ij} \mid b_{ij}, X_{ij}\right) = X_{ij}\beta^C + b_{ij}$$

$$b_{ij} \mid X_i \sim N\left(0, D\right)$$

Regression parameters have been termed "subject-specific" and for time-varying (varying within subject) covariates have simple interpretation.

For random intercept model, they measure change in individual's odds of response associated with a change in covariates.

For time-invariate covariate the interpretation can be difficult or misleading because they measure contrast in covariate holding random effect constant. With generalized models, the magnitude and interpretation of such coefficients depends entirely on random effects model assumptions.

More on Marginal Models

Model:

$$\text{logit}E\left(Y_{ij} \mid X_{ij}\right) = \text{logit}\left(\mu_{ij}\right) = X_{ij}\beta^M$$

$$Var\left(Y_{ij} \mid X_{ij}\right) = \phi\nu\left(\mu_{ij}\right)$$

The term "marginal mean" refers to the fact that we are not conditioning on other response variables or unobserved random effects.

Marginal means can be interpreted as averaging over both measurement errors and random interindividual heterogeneity.

Marginalized Multilevel Models

P. Heagerty "Marginally Specified Logistic-Normal Models for Longitudinal Binary Data" Biometrics, 1999

P. Heagerty and S. Zeger "Marginalized Multilevel Models and Likelihood Inference" Statistical Science, 2000

Model:

$$\text{logit}\, E\left(Y_{ij} \mid X_{ij}\right) = X_{ij}\beta \qquad (1)$$

$$\text{logit}\, E\left(Y_{ij} \mid b_{ij}, X_{ij}\right) = \Delta_{ij} + b_{ij} \qquad (2)$$

$$b_i \mid X_i \sim N\left(0, D_i\right)$$

(1) – marginal logistic regression for the average response as a function of covariates

(2) – model for dependence is a conditional model on random effects

Marginalized Multilevel Models (cont)

Δ_{ij} is a function of both the marginal linear predictor $X_{ij}\beta$ and the random effect distribution

$$h\left(X_{ij}\beta\right)=\int h\left(\Delta_{ij}+b_{ij}\right)dF_{\alpha}\left(b_{ij}\right)$$

Integral equation that links marginal and conditional regression parameters

Can be solved for Δ_{ij} using numerical integration and Newton-Raphson iteration

MMM Interpretation

- The parameters are interpreted as contrasting the log odds of success for subgroups defined by measured covariates
- For a single binary covariate X_{ij1}

$$\beta_1 = \text{logit}\, E\left(Y_{ij} \mid X_{ij1} = 1\right) - \text{logit}\, E\left(Y_{i'j'} \mid X_{i'j'1} = 0\right)$$

measures the variation in success log odds “between groups”

- The model explicitly assumes individual heterogeneity but for the group contrast β_1 , we average over this distribution within each subgroup

Interpretation of heterogeneity parameters

$$g\left(E\left(Y_i \mid X_i, b_i\right)\right) = X_i\beta^* + Z_i b_i$$

In the simplest model: random intercept model

$$b_{ij} = b_{i0} \sim N\left(0, \sigma^2\right)$$

$$b_{ij} = \sigma z_i,\ z_i \sim N\left(0,1\right)$$

Then the conditional model becomes:

$$\text{logit}\, E\left(Y_{ij} \mid b_{ij}, X_{ij}\right) = \Delta_{ij} + \sigma z_i$$

σ can be interpreted as a regression coefficient for a standardized omitted covariate. Measures magnitude of variation in log odds between individuals within a group

Model Estimation

Maximum Likelihood

The likelihood contribution can be constructed by the assumption of conditional independence of observations on random effect.

Estimating Equations (Quadratic)

Specification of marginal mean model and a 'working model' for the marginal covariance. The primary advantage: inference about β can be made robust to incorrect specification of the within-subject dependence model.

Provides feasible estimation even for high-dimensional problems.

Ubiquitous phenomenon of missing data

MCAR with QEE versus MAR with likelihood approach

Example

The Madras longitudinal schizophrenia study followed 90 first-episode schizophrenics for 10 years (Thara et al., 1994)

Data: Apathy symptom (present or not) measured monthly for the first year

Objective: differences with respect to age at onset (age > 20 years) and gender.

Model:

Marginal mean $\text{logit}\left(E\left(Y_{ij} \mid X_i\right)\right) = \beta_0 + \beta_1\left(t_j - 6\right) + \beta_2 Age_i + \beta_3 Female_i$

Heterogeneity $\text{logit}\left(E\left(Y_{ij} \mid X_i, b_i\right)\right) = \Delta_{ij} + b_i$

$$b_i \mid X_i \sim N\left(0, \sigma_i^2\right)$$

$$\log\left(\sigma_i\right) = \alpha_0 + \alpha_1 Female_i$$

Models allows for different heterogeneity depending on gender

Example

	Marginal/ Likelihood		Marginal/QEE			Conditional/Likelihood	
	Estimate	Model SE	Estimate	Model SE	Empirical SE	Estimate	Model SE
Mean							
Intercept	-1.945	0.242	-2.120	0.404	0.381	-4.300	0.644
Time	-0.209	0.028	-0.236	0.031	0.040	-0.374	0.044
Age	0.494	0.247	0.505	0.357	0.347	0.820	0.482
Female	-0.026	0.265	0.089	0.354	0.339	1.202	0.605
Log(σ)							
Intercept	1.408	0.189	1.365		0.505	1.300	0.149
Female	-0.853	0.267	-0.996		0.576	-0.727	0.235

Conditional model

$$\text{logit}\left(E\left(Y_{ij} \mid X_i, b_i\right)\right) = \beta_0^C + \beta_1^C\left(t_j - 6\right) + \beta_2^C Age_i + \beta_3^C Female_i + b_i$$

Example

	Conditional/Likelihood	
	Estimate	**Model SE**
Mean		
Intercept	-4.300	0.644
Time	-0.374	0.044
Age	0.820	0.482
Female	1.202	0.605
Log(σ)		
Intercept	1.300	0.149
Female	-0.727	0.235

Conditional model

$$\text{logit}\left(E\left(Y_{ij} \mid X_i, b_i\right)\right) = \beta_0^C + \beta_1^C\left(t_j - 6\right) + \beta_2^C Age_i + \beta_3^C Female_i + b_i$$

Positive gender effect on odds of Apathy from conditional estimation

Marginal probability of outcome calculated from conditional model:

Among males:

$$\int h\left(-4.300 + 3.699z\right)\phi\left(z\right)dz = 0.146$$

Among females:

$$\int h\left(-4.300 + 1.202 + 1.773z\right)\phi\left(z\right)dz = 0.107$$

The observed positive gender effect from conditional model is not implied in aggregate due to the differences in the degree of between-subject variation between genders

Practical Aspect

Choice of statistical method depends on both the primary research question and available software.

Every conditional model implies a marginal model via integration over the dependence structure.

$$X\beta = h_M^{-1}\left(\int h_C\left(\Delta + b\right) dF_\alpha\left(b\right)\right)$$

$$\Delta_{ij} = \Delta_{ij}\left(X_{ij}, \beta, b_i, F_\alpha\left(b_{ij}\right)\right)$$

Griswold (2004 and 2013) derived expression for some MMM models:

1. Logistic-Logistic-Normal
2. Logistic-Probit-Normal
3. Logistic-Logistic-Bridge
4. Log-Log-Gamma

Crossover Trial SAS Code

Source: M. Griswold and S. Zeger, 2004

```
data xover;
input id Period Treatment y count @@;  cards;
1 0 1 1 22   1 1 0 1 22   2 0 1 0  0   2 1 0 1  0
3 0 1 1  6   3 1 0 0  6   4 0 1 0 6  4 1 0 0 6
5 0 0 1 18   5 1 1 1 18   6 0 0 0 4   6 1 1 1  4
7 0 0 1  2   7 1 1 0  2   8 0 0 0 9  8 1 1 0 9
;
run;

TITLE   "Logit-Probit-Normal MMM";
PROC NLMIXED data=xover qpoints=100;
PARMS  alpha0_m=.6  alpha1_m=.6  alpha2_m=-.3  tau=3;
eta_m = alpha0_m + alpha1_m*Treatment + alpha2_m*Period;
pi_m = 1 / (1 + exp(-eta_m));
delta  =  sqrt(1+(tau*tau))  *  probit(pi_m); eta_c   =   delta + a;
pi_c  =  probnorm(eta_c);
MODEL y ~ binary(pi_c);
RANDOM a ~ NORMAL(0,tau*tau) SUBJECT=id;
REPLICATE count;
run;
```

Requires many more quadrature points to obtain stable variance estimate.

Summary

Marginalized multilevel models

- Have interpretation and robustness of a marginal model
- Retain likelihood inference capabilities and flexible dependence specification from GLMM
- Relax MCAR assumption

Literature

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Thank you!