

Generalized Linear Mixed Models with Random Effects

- The logistic regression model with random intercept
Example: 2×2 crossover trial
Example: Indonesian Children Health Study
- The Poisson regression model with random intercept
Example: seizure data

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Random Effects GLM

The basic idea: there is natural heterogeneity among subjects.

- Systematic part

$$g(E[Y_{ij} | U_i]) = \beta_0 + \beta_1 x_{ij} + U_i$$

- Random Part

$$\begin{aligned}
 Y_{ij} | U_i &\sim \text{GLM} \\
 &\quad \text{Normal} \\
 &\quad \text{Bernoulli} \\
 &\quad \text{Poisson} \\
 U_i &\sim N(0, G)
 \end{aligned}$$

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Example: 2×2 crossover trial

In random effects models, the regression coefficients measure the more direct influence of explanatory variables on the responses for heterogeneous individuals. For example

$$\begin{aligned}
 \text{logit}P(Y_{ij} | U_i) &= \beta_0^* + U_i + \beta_1^* x_{ij} \\
 x_{ij} &= \begin{cases} 1 & \text{treat. A} \\ 0 & \text{plac. B} \end{cases}
 \end{aligned}$$

This model states that:

1. each person has their own probability of positive response under a placebo (B)

$$P(Y_{ij} = 1 | U_i, x_{ij} = 0) = \frac{\exp(\beta_0^* + U_i)}{1 + \exp(\beta_0^* + U_i)}$$

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2. a person's odds of a normal response are multiplied by $\exp(\beta_1^*)$ when taking the drug A, regardless of the initial risk

$$\begin{aligned}
 \frac{P(Y_{ij}=1|U_i, x_{ij}=0)}{P(Y_{ij}=0|U_i, x_{ij}=0)} &= \exp(\beta_0^* + U_i) \\
 \frac{P(Y_{ij}=1|U_i, x_{ij}=1)}{P(Y_{ij}=0|U_i, x_{ij}=1)} &= \exp(\beta_0^* + \beta_1^* + U_i) \\
 \frac{P(Y_{ij}=1|U_i, x_{ij}=1)}{P(Y_{ij}=0|U_i, x_{ij}=1)} &= \frac{P(Y_{ij}=1|U_i, x_{ij}=0)}{P(Y_{ij}=0|U_i, x_{ij}=0)} \exp(\beta_1^*)
 \end{aligned}$$

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In Logistic Models

1. $|\beta| \leq |\beta^*|$
2. $\beta = \beta^*$ if and only if $VarU_i = 0$
3. $\hat{\beta}/se(\hat{\beta}) = \hat{\beta}^*/se(\hat{\beta}^*)$
4. Marginal Model estimates smaller than random effects estimates
5. Tests of hypotheses approximately the same

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Correspondence between regression parameters in random effects and marginal models

- let β the vector of regression coefficients under a marginal model
- let β^* the vector of regression coefficients under a random effects model
- G is the variance of the random effects

$$\beta \simeq (0.346G^2 + 1)^{-1/2} \beta^*$$

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Estimation of Generalized Linear Mixed Models

- $f(Y_{ij} | U_i)$ in the exponential family
- $Y_{i1}, \dots, Y_{in_i} | U_i$ are independent
- $U_i \sim f(U_i, G)$
- **Maximum Likelihood**

U_i is a set of unobserved variables which we integrate out of the likelihood

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Maximum Likelihood estimation of G and β

1. We will treat $U_i \sim N(0, G)$ we can learn about one individual's coefficients by understanding the variability in coefficients across the population
2. if G_i is small \rightarrow rely on population average coefficients to estimate those for an individual
we weight the cross-sectional information more heavily and we borrow strength across subjects
3. if G_i is large \rightarrow rely more heavily on the data from each individual in estimating their own coefficients
we weight the longitudinal information more heavily since comparisons within a subject are likely to be more precise than comparisons among subjects.

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Maximum likelihood estimation

“averaged-away” the random effects

$$\underbrace{L(\beta, G, \mathbf{Y})}_{\text{what we see}} =$$

$$= \prod_{i=1}^m \int \prod_{j=1}^{n_i} \underbrace{Pr(Y_{ij} | U_i, \beta)}_{\text{what we think exists}} f(U_i, G) dU_i$$

- Used all the data
- EM algorithm
- Numerical integration

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Maximum Likelihood

Example: 2 × 2 crossover trial

$$\begin{aligned} \text{logit}P(Y_{ij} = 1 | U_i) &= \beta_0 + U_i + \beta_1 x_{ij1} + \beta_2 x_{ij2} \\ U_i &\sim N(0, G) \end{aligned}$$

- $x_{ij1} = 1$ if active drug (A) or 0 if placebo (B)
- $x_{ij2} = 1$ if period 2 or 0 if period 1
- $\sqrt{\hat{G}} = 4.9$: 95% of the subjects would fall between $(-2 \times 4.9, 2 \times 4.9)$ logit units of the overall mean.
- This range on the logit scale translates into probabilities between 0 and 1, i.e. some people have little chance and others have very high chance of a normal reading in the placebo and the treatment group.
- Assuming a constant treatment effect for all persons, the odds of a normal response for a subject are estimated to be $\exp(\hat{\beta}_1) = \exp(1.9) = 6.7$ times higher on the active drug than on the placebo.

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In Summary

Example: 2 × 2 crossover trial

- Marginal Model $\hat{\beta}_1 = 0.57(0.23)$, $\exp(0.57) \simeq 2$
- Random effects Model (maximum likelihood) $\hat{\beta}_1 = 1.9(0.91)$, $\exp(1.9) \simeq 7$, $\hat{G} = 4.9$
- The smaller value from the marginal analysis is consistent with the theoretical inequality: $(0.346\hat{G} + 1)^{1/2} = 3.1$

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Indonesian Study - Maximum Likelihood approach

With a random effect model, here we can address the question of how an individual child's risk for respiratory infection will change if their vitamin A status were to change.

- we assume that each child have a distinct intercept which represents their propensity to infection
- we have accounted for correlation by including random intercepts $U_i \sim N(0, G)$
- $\sqrt{\hat{G}} = 0.72 \Rightarrow$ considerable heterogeneity among children
- Among children with linear predictor equal to the intercept -2.2 (average age, height, female, vitamin A sufficient), about 95% would have a probability of infection between 0.03 and 0.31:

$$P(Y_{ij} = 1 | U_i = -2 \times 0.72) = \frac{\exp(-2.2 - 2 \times 0.72)}{1 + \exp(-2.2 - 2 \times 0.72)} = 0.025$$

$$P(Y_{ij} = 1 | U_i = +2 \times 0.72) = \frac{\exp(-2.2 + 2 \times 0.72)}{1 + \exp(-2.2 + 2 \times 0.72)} = 0.31$$
- relative odds of infection associated with vitamin A deficiency are $\exp(0.54) = 1.7$

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- the longitudinal age effect on the risk of RI in Model 2, can be explained by the seasonal trend in model 3
- Because of the small heterogeneity the estimates of the coefficients obtained under a random effects models are similar to the marginal model coefficients
- the ratio of the RE coefficients and marginal coefficients are close to $(0.346\hat{G} + 1)^{1/2}$

**Poisson model with random intercept:
Epileptic seizure example**

$$\log E(Y_{ij} | \gamma_i) = \gamma_i + \beta_1 x_{ij1} + \beta_2 x_{ij2} + \beta_3 x_{ij1} x_{ij2} + \log(t_{ij})$$

$$j = 0, 1, \dots, 4$$

$$i = 1, \dots, 59$$

$$\gamma_i = \beta_0 + U_i$$

where

$$x_{ij1} = \begin{cases} 1 & \text{if the } i\text{th subject is assigned to the prog. group} \\ 0 & \text{if the } i\text{th subject is assigned to the pla. group} \end{cases}$$

$$x_{ij2} = \begin{cases} 1 & \text{if } j = 1, 2, 3, 4 \\ 0 & \text{if } j = 0. \end{cases}$$

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Seizure Example

Group	Visit	Expected # seizures
Placebo ($x_1 = 0$)	0 ($x_2 = 0$)	$8 \exp(\gamma_i)$
Placebo ($x_1 = 0$)	1,2,3,4 ($x_2 = 1$)	$2 \exp(\gamma_i + \beta_2)$
Progabide ($x_1 = 1$)	0 ($x_2 = 0$)	$8 \exp(\gamma_i + \beta_1)$
Progabide ($x_1 = 1$)	1,2,3,4 ($x_2 = 1$)	$2 \exp(\gamma_i + \beta_1 + \beta_2 + \beta_3)$

- $t_{i0} = 8$
- $t_{i1} = t_{i2} = t_{i3} = t_{i4} = 2$

- $\exp(\gamma_i)$ is the expected baseline seizure count for the i th subject, $i = 1, \dots, 59$

$$E[Y_{ij} | U_i, x_1 = 0, x_2 = 0] / 8 = \exp(\gamma_i)$$

- β_2 represents the log ratio of the seizure rates post versus pre-randomization for the placebo group (*same for each subject*):

$$\frac{(E[Y_{ij} | U_i, x_1 = 0, x_2 = 1] / 2)}{(E[Y_{ij} | U_i, x_1 = 0, x_2 = 0] / 8)} = \frac{\exp(\gamma_i + \beta_2)}{\exp(\gamma_i)} = \exp(\beta_2)$$

- $\beta_2 + \beta_3$ represents the log ratio of the seizure rates post versus pre-randomization for the treatment group (*same for each subject*):

$$\frac{(E[Y_{ij} | U_i, x_1 = 1, x_2 = 1] / 2)}{(E[Y_{ij} | U_i, x_1 = 1, x_2 = 0] / 2)} = \frac{\exp(\gamma_i + \beta_1 + \beta_2 + \beta_3)}{\exp(\gamma_i + \beta_1)} = \exp(\beta_2 + \beta_3)$$

- $\exp(\beta_3)$ represents the ratio of seizure rates post versus pre-randomization for the treatment group divided by seizure rates post versus pre-randomization for the control group.
- a negative value of β_3 indicates that a relatively larger fraction of the total seizures in the treatment group occurred before rather

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than after randomization as compared to the placebo group. (i.e. the treatment is effective)

- $\hat{\beta}_3 = -0.10(0.065)$ (modest evidence that the progabide is effective)
- the model doesn't fit well
- extend the model by including a random slope U_{i2}

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Poisson-Gaussian random effects models: Epileptic seizure

$$\log E(Y_{ij} | U_{i1}, U_{i2}) = \beta_0 + \beta_1 x_{ij1} + \beta_2 x_{ij2} + \beta_3 x_{ij1} x_{ij2} + U_{i1} + U_{i2} x_{ij2} + \log(t_{ij})$$

$$(U_{i1}, U_{i2}) \sim N \left((0, 0), \begin{bmatrix} G_{11} & G_{12} \\ G_{21} & G_{22} \end{bmatrix} \right)$$

- here we are assuming that there might be heterogeneity among subjects in the ratio of the expected seizure counts before and after the randomization.
- the degree of heterogeneity can be measured by G_{22}
- maximum likelihood estimation
- ratio of seizure counts in the placebo post-to-pre treatment is subject specific

$$\frac{(E[Y_{ij}|U_{i1}, U_{i2}, x_1=0, x_2=1]/2)}{(E[Y_{ij}|U_{i1}, U_{i2}, x_1=0, x_2=0]/2)} = \frac{\exp(\beta_0 + U_{i1} + \beta_2 + U_{i2})}{\exp(\beta_0 + U_{i1})} = \exp(\beta_2 + U_{i2})$$

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- ratio of seizure counts in the progabide group post-to-pre treatment is subject specific

$$\frac{(E[Y_{ij}|U_{i1}, U_{i2}, x_1=1, x_2=1]/2)}{(E[Y_{ij}|U_{i1}, U_{i2}, x_1=1, x_2=0]/2)} = \frac{\exp(\beta_0 + U_{i1} + \beta_1 + \beta_2 + U_{i2} + \beta_3)}{\exp(\beta_0 + U_{i1} + \beta_1)} = \exp(\beta_2 + U_{i2} + \beta_3)$$

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Results

- The estimate of G_{22} is statistical significant, therefore the data give support of between subject variability in the the ratio of the expected seizure counts before and after the randomization.
- $\exp(\hat{\beta}_2) = \exp(0.002) = 1.002$ subjects in the placebo group with $U_{i2} = 0$ have expected seizure rates after the treatment which are estimated to be roughly the same as before treatment.
- Subjects in the progabide group with $U_{i2} = 0$, the seizure rates are reduced after the treatment by about 27% ($1 - \exp(\hat{\beta}_2 + \hat{\beta}_3) = (1 - \exp(0.002 - 0.31)) = 0.27$)
- the treatment seems to have a modest effect: $\hat{\beta}_3 = -0.31, (0.15)$
- without patient 207 the evidence of the progabide is stronger $\hat{\beta}_3 = -0.34(0.15)$

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