Lecture 10 | 13.05.2024

Generalized linear models
with random effects

GLM extensions for the longitudinal data

- **Marginal models**
  - primary interest is given to the conditional mean structure
  - separate model for the mean and the correlated observations

- **Random effects models**
  - one equation used to account for both—the mean and the correlation
  - mostly used when subject specific inference is of some interest

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  - the correlation structure due to historical observations within the model

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All three categories of the regression models for correlated (repeated) observations lead to the same model (with the same interpretation) for the Gaussian type of the data but for the discrete data different models can produce different interpretations (due to non-linearity involved)

Random effects models

- **Mean structure**

$$\mu_{ij} = E[Y_{ij}|\boldsymbol{X}_{ij}, \boldsymbol{w}_i] = \psi'(\theta_{ij})$$

- **Variance structure**

$$v_{ij} = Var[Y_{ij}|\boldsymbol{X}_{ij}, \boldsymbol{w}_i] = \psi''(\theta_{ij})\phi$$

where we assume the exponential family for the conditional distribution of $Y_{ij}|(\boldsymbol{X}_{ij}, \boldsymbol{w}_i)$ with $f_{(Y|\boldsymbol{X}_{ij}, \boldsymbol{w}_i)}(y) = \exp\{[y\theta_{ij} - \psi(\theta_{ij})]/\phi + c(y, \phi)\}$, where $g(\mu_{ij}) = \boldsymbol{X}_{ij}^\top \beta + \boldsymbol{Z}_{ij}^\top \boldsymbol{w}_i$ and $v_{ij} = v(\mu_{ij})\phi$ (link and variance functions)

- **Covariance structure**
  Determined by random effects $\boldsymbol{w}_1, \dots, \boldsymbol{w}_N$ which are independent with some common underlying distribution and the subject specific responses $Y_{i1}, \dots, Y_{in_i}$ are, conditionally on $\boldsymbol{w}_i$, independent

Generalized linear mixed models (GLMM)

- for a subject specific response vector $\boldsymbol{Y}_i = (Y_{i1}, \dots, Y_{in_i})^\top$ and explanatory vectors of covariates $\mathbb{X}_i = (\boldsymbol{X}_{i1}, \dots, \boldsymbol{X}_{in_i})^\top \in \mathbb{R}^{n_1 \times p}$ it is assumed that responses Y_{ij} for $j = 1, \dots, n_i$, are, given the random effects $\boldsymbol{w}_i \in \mathbb{R}^r$, independent with the density function,

$$f(y|\boldsymbol{X}_{ij}, \boldsymbol{w}_i) = \exp\{\phi^{-1}[y\theta_{ij} - \psi(\theta_{ij})] + c(y, \phi)\}, \quad \text{for } y \in \mathbb{R}$$

  where, in addition, it holds that
  - canonical parameter $\theta_{ij} = \boldsymbol{X}_{ij}^\top \beta + \boldsymbol{Z}_{ij}^\top \boldsymbol{w}_i$
  - random effects follow the Gaussian distribution $\boldsymbol{w}_i \sim N_r(\boldsymbol{0}, \mathbb{G})$
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- thus, for the whole subject's specific vector $\boldsymbol{Y}_i$ given $\mathbb{X}_i$ and the random effects in $\boldsymbol{w}_i$ we obtain the conditional density of $\boldsymbol{Y}_i|(\mathbb{X}_i, \boldsymbol{w}_i)$

$$f_i(\boldsymbol{y}|\mathbb{X}_i, \boldsymbol{w}_i) = \prod_{j=1}^{n_i} f(y_j|\boldsymbol{X}_{ij}, \boldsymbol{w}_i), \quad \text{for } \boldsymbol{y} = (y_1, \dots, y_{n_i})^\top \in \mathbb{R}^{n_i}$$

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Note, that both densities still depend on $\beta \in \mathbb{R}^p$ and $\phi > 0$ thus, we have a fully specified parametric model—the notation, for brevity, does not reflect this dependence

From hierarchical to marginal model

- Note, that the model specification is given in terms of a hierarchical model (two hierarchical model equations)

$$Y_{ij}|(\boldsymbol{X}_{ij}, \boldsymbol{w}_i) \sim f(y|\boldsymbol{X}_{ij}, \boldsymbol{w}_i) \quad \text{and} \quad \boldsymbol{w}_i \sim N_r(\boldsymbol{0}, \mathbb{G})$$

  and, analogously, also

$$\boldsymbol{Y}_i|(\mathbb{X}_i, \boldsymbol{w}_i) \sim f_i(\boldsymbol{y}|\mathbb{X}_i, \boldsymbol{w}_i) \quad \text{and} \quad \boldsymbol{w}_i \sim N_r(\boldsymbol{0}, \mathbb{G})$$

- The marginal model $f(\boldsymbol{y}|\mathbb{X}_i)$ is obtained by integrating over $\boldsymbol{w}_i \sim N_r(\boldsymbol{0}, \mathbb{G})$ which gives the marginal (conditional) density (population interpretation)

$$f_i(\boldsymbol{y}|\mathbb{X}_i) = \int_{\mathbb{R}^r} f_i(\boldsymbol{y}|\mathbb{X}_i, \boldsymbol{w}) \mathrm{d}\Phi(\boldsymbol{w}) = \int_{\mathbb{R}^r} \prod_{j=1}^{n_i} f(y_j|\boldsymbol{X}_{ij}, \boldsymbol{w}) f_\Phi(\boldsymbol{w}) \mathrm{d}\boldsymbol{w}$$

  where $\Phi(\cdot)$ is the distribution function of the Gaussian $N_r(\boldsymbol{0}, \mathbb{G})$ distribution and f_Φ is the corresponding density function

GLMM Likelihood and log-likelihood

- the marginal distribution of $\boldsymbol{Y}_i$ (conditionally on $\mathbb{X}_i$) depends on unknown (mean structure) parameters $\boldsymbol{\beta} \in \mathbb{R}^p$, the over-dispersion parameter $\phi > 0$, and a (positive-definite) variance-covariance matrix $\mathbb{G} \in \mathbb{R}^{r \times r}$
- thus, given the longitudinal observations in $\mathcal{D} = \{(\boldsymbol{Y}_i, \mathbb{X}_i);\ i = 1, \dots, N\}$ the full likelihood for $\boldsymbol{\beta}, \phi$, and $\mathbb{G}$ can be expressed as

$$L(\boldsymbol{\beta}, \mathbb{G}, \phi, \mathcal{D}) = \prod_{i=1}^{N} f_i(\boldsymbol{Y}_i | \mathbb{X}_i)$$

$$= \prod_{i=1}^{N} \int_{\mathbb{R}^r} \prod_{j=1}^{n_i} f(y_j | \boldsymbol{X}_{ij}, \boldsymbol{w}) f_{\Phi}(\boldsymbol{w}) \mathrm{d}\boldsymbol{w}$$

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- Under the normal linear model, the integral(s) can be worked out analytically but, in general, various (numerical) approximations are needed to obtain the final solution
- Subject specific interpretation can be carried out in terms of the random effects predictions based on the posterior distribution $f(\boldsymbol{w}_i | \boldsymbol{Y}_i, \mathbb{X}_i)$

Computational issues and approximations

Basically, three types of numerical approximations are typically used...

- approximation of the integrand
- approximation of the data
- approximation of the integral

Laplace approximation of the integrand

- the integral(s) in the likelihood $L(\beta, \mathbb{G}, \phi, \mathcal{D})$ can be equivalently rewritten in a form $\int e^{Q(\boldsymbol{w})}\mathrm{d}\boldsymbol{w}$ and the second order Taylor expansion can be applied to approximate $Q(\boldsymbol{w})$
- expansion around the mode $\overline{\boldsymbol{w}} \in \mathbb{R}^r$ as

$$Q(\boldsymbol{w}) \approx Q(\overline{\boldsymbol{w}}) + \frac{1}{2}(\boldsymbol{w} - \overline{\boldsymbol{w}})^\top Q''(\overline{\boldsymbol{w}})(\boldsymbol{w} - \overline{\boldsymbol{w}})$$

- provides reasonably good approximation in case of many repeated measurements per each subject

Approximation of the data

- The GLMM model $g(\mu_{ij}) = g(E[Y_{ij}|\boldsymbol{X}_{ij}, \boldsymbol{w}_i]) = \boldsymbol{X}_{ij}^\top \beta + \boldsymbol{Z}_{ij}^\top \boldsymbol{w}_i$ is rewritten (approximated) in a form

$$Y_{ij} = g^{-1}(\boldsymbol{X}_{ij}^\top \beta + \boldsymbol{Z}_{ij}^\top \boldsymbol{w}_i) + \varepsilon_{ij}$$

  where $\varepsilon_{ij} \sim (0, \phi v(\mu_{ij}))$ and the Taylor expansion is applied to μ_{ij}

- First order Taylor expansion
  - around current values of $\widehat{\beta}$ and $\widehat{\boldsymbol{w}}_i$ — Penalized quasi-likelihood (PQL)
  - around current values of $\widehat{\beta}$ and $\widehat{\boldsymbol{w}}_i = \boldsymbol{0}$ — Marginal quasi-likelihood (MQL)

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- MQL only performs relatively well if the random effects variance is small
- Both, PQL and MQL perform bad for binary data with only few observations per subject
- For increasing number of measurements within each subject MQL remains biased while PQL is consistent

Approximation of the integral

- The likelihood contribution of each subject is

$$f_i(\boldsymbol{Y}_i|\mathbb{X}_i) = \int_{\mathbb{R}^r} \prod_{j=1}^{n_i} f(y_j|\boldsymbol{X}_{ij}, \boldsymbol{w}) f_\Phi(\boldsymbol{w}) \mathrm{d}\boldsymbol{w} = \int f(\boldsymbol{w}) f_\Phi(\boldsymbol{w}) \mathrm{d}\boldsymbol{w}$$

- Gaussian quadrature method is used to approximate the last integral above in a way

$$\int f(\boldsymbol{w}) f_\Phi(\boldsymbol{w}) \mathrm{d}\boldsymbol{w} \approx \sum_{q=1}^{Q} \omega_q f(\boldsymbol{w}_q)$$

  for some weights $\omega_q > 0$ and nodes $\boldsymbol{w}_q$, for $q = 1, \ldots, Q$

- Gaussian quadrature uses nodes and waights that are fixed and adaptive Gaussian quadrature adjust the nodes and the weights to adapt to the support of $f(\boldsymbol{w}) f_\Phi(\boldsymbol{w})$ (but it is also more time consuming) (addaptive Gaussian quadrature with $Q = 1$ is equivalent with the Laplace approximation)

Parameter interpretation

- The parameter vector $\beta \in \mathbb{R}^p$ is interpreted differently in GEE model (marginal interpretation) and GLMM model (conditional interpretation)
- In general, the marginal model is not of the same parametric form as the conditonal average in the GLMM formulation
- For logistic mixed regression model in particular (with a normally distributed random intercept) it can be shown that the marginal model can be well approximated by another logistic (marginal) model, however, with the parameters $\widehat{\beta}^{\mathsf{GLMM}} = \sqrt{c^2\sigma^2 + 1}\widehat{\beta}^{\mathsf{M}}$ where σ^2 is the variance of the random intercept and $c \approx 16\sqrt{3}/(15\pi)$
- In practice, the marginal interpretation can be derived from the GLMM output by integrating out the random effects part of the model which can be done numerically, for instance, by the Gaussian quadrature or sampling methods

Summary

- GLM models with random effects are particularly suitable in situations where subject specific inference is of interest
- Underlying theory and the estimation is based on maximum likelihood and its properties (quasilikelihood and marginal likelihood)
- Different computational approaches and algorithms are used to obtain the solution—the estimates of the fixed effect parameters
- Marginal form of the GLM model with random effects has, generally, different interpretation of the parameters than the marginal model
- The right choice of the model always depends on the question of interest, the underlying data, and the sole purpose of the model