

# 1 Nonlinear Mixed Effects Model

## 1.1 The model

(Lindstrom & Bates, 1990) proposed a nonlinear mixed effects model which is a combination of the nonlinear fixed effects model and the linear mixed effects model. In this model, the assumption of normal errors holds and the expectation function is nonlinear.

The nonlinear mixed effect model for the  $i_{th}$  individual at the  $j_{th}$  observation time can be defined as

$$y_{ij} = f(\phi_i, \mathbf{x}_{ij}) + e_{ij}, \quad (1.1)$$

where  $Y_{ij}$  is the  $i_{th}$  individual's response at time  $j$ ,  $f$  is a nonlinear function of the parameter vector  $\phi_i$  and the predictor vector  $\mathbf{x}_{ij}$  and  $e_{ij}$  is the error term which is normally distributed. The model allows individuals to have different parameter vectors by writing  $\phi_i$  as

$$\phi_i = \mathbf{A}_i\beta + \mathbf{B}_i\mathbf{b}_i \quad (1.2)$$

where  $\beta$  is the vector of fixed effects,  $\mathbf{b}_i \sim N(\mathbf{0}, \sigma^2 \mathbf{D})$  is the vector of random effects,  $\mathbf{A}_i$  and  $\mathbf{B}_i$  are design matrices for the fixed and random effects, respectively. The inclusion of matrices  $\mathbf{A}_i$  and  $\mathbf{B}_i$  gives a flexible model specification. For example, if  $\mathbf{A}_i = [\mathbf{I}, \mathbf{0}]$  for subjects in group 1 and  $\mathbf{A}_i = [\mathbf{0}, \mathbf{I}]$  for subjects in group 2 then the two groups will have different fixed effects. Similarly, the columns in  $\mathbf{B}_i$  can control the components of random effects.

The model for the  $i_{th}$  subject's can be written as

$$\mathbf{y}_i = \boldsymbol{\eta}_i(\phi_i) + \mathbf{e}_i \quad (1.3)$$

where  $\mathbf{y}_i = [y_{i1}, y_{i2}, \dots, y_{in_i}]^T$ ,  $\mathbf{e}_i = [e_{i1}, e_{i2}, \dots, e_{in_i}]^T$ ,  $\mathbf{e}_i \sim N(\mathbf{0}, \sigma^2 \mathbf{\Lambda}_i)$  and  $\boldsymbol{\eta}_i(\phi_i) = [f(\phi_i, \mathbf{x}_{i1}), f(\phi_i, \mathbf{x}_{i2}), \dots, f(\phi_i, \mathbf{x}_{in_i})]^T$ .  $\mathbf{\Lambda}_i$  depends on  $i$  only through its dimension. In many cases  $\mathbf{\Lambda}_i = \mathbf{I}$  but nonindependent covariance matrices are also allowed.

We can incorporate models for  $N$  subjects into one model by letting  $\mathbf{y} = [\mathbf{y}_1, \mathbf{y}_2, \dots, \mathbf{y}_N]^T$ ,  $\phi = [\phi_1, \phi_2, \dots, \phi_N]^T$ , and  $\boldsymbol{\eta}(\phi) = [\boldsymbol{\eta}_1(\phi_1), \boldsymbol{\eta}_2(\phi_2), \dots, \boldsymbol{\eta}_N(\phi_N)]$ . Then the overall model can be written as

$$\begin{aligned} \mathbf{y}|\mathbf{b} &\sim N(\boldsymbol{\eta}(\phi), \sigma^2 \mathbf{\Lambda}), \\ \phi &= \mathbf{A}\beta + \mathbf{B}\mathbf{b}, \\ \mathbf{b} &\sim N(\mathbf{0}, \sigma^2 \tilde{\mathbf{D}}) \end{aligned} \quad (1.4)$$

where  $\tilde{D} = \text{diag}(D, D, \dots, D)$ ,  $\Lambda = \text{diag}(\Lambda_1, \Lambda_2, \dots, \Lambda_N)$ ,  $B = \text{diag}(B_1, B_2, \dots, B_N)$ ,  $A = [A_1, A_2, \dots, A_N]^T$  and  $b = [b_1, b_2, \dots, b_N]^T$ .

## 1.2 Estimation

The estimates (Lindstrom & Bates, 1990) proposed are maximum likelihood estimates for fixed effects and posterior modes for random effects.

Let  $\theta$  contain the parameters in  $D$  and  $\Lambda$ . The estimator  $\hat{\beta}(\theta)$  and  $\hat{b}(\theta)$  maximize the following function:

$$g(\beta, b|y) = -1/2\sigma^{-2}(y - \eta(A\beta + Bb))^T \Lambda^{-1}(y - \eta(A\beta + Bb)) - 1/2\sigma^{-2}b^T \tilde{D}^{-1}b. \quad (1.5)$$

If  $\beta$  is fixed then the  $b$  that maximizes  $g$  is the posterior mode since  $g$  is a posterior density of  $b$  plus a constant for a given  $\beta$ . The estimates can be obtained by first creating a 'pseudo-data'

$$\tilde{y} = \tilde{\eta}(A\beta + Bb) + \tilde{e}, \quad (1.6)$$

where  $\tilde{y} = \begin{bmatrix} \eta^{-1/2}y \\ \mathbf{0} \end{bmatrix}$ ,  $\tilde{e} \sim N(0, \sigma^2 I)$  and  $\tilde{\eta}(A\beta + Bb) = \begin{bmatrix} \Lambda^{1/2}\eta(A\beta + Bb) \\ \tilde{D}^{-1/2}b \end{bmatrix}$ . The estimates can then be calculated using the least squares approach.

The maximum likelihood estimators for  $\theta$  based on the marginal density of  $y$  is very difficult to obtain since  $\eta$  is nonlinear in  $b$ . (Lindstrom & Bates, 1990) instead approximated the marginal distribution of  $y$  by

$$y \sim N(\eta(A\beta + B\hat{b}) - \hat{Z}\hat{b}, \sigma^2 \hat{V}), \quad (1.7)$$

where  $\hat{V} = \Lambda + \hat{Z}\tilde{D}\hat{Z}^T$ , and  $\hat{Z} = \frac{\partial \eta}{\partial b^T}|_{\beta, \hat{b}}$ . The log-likelihood to the approximate marginal distribution can then be obtained as

$$l(\beta, \sigma, \theta|y) = -\frac{1}{2}\log|\sigma^2 \hat{V}| - \frac{1}{2\sigma^2}[y - \eta(A\beta + B\hat{b}) + \hat{Z}\hat{b}]^T \hat{V}^{-1}[y - \eta(A\beta + B\hat{b}) + \hat{Z}\hat{b}]. \quad (1.8)$$

The estimators (Lindstrom & Bates, 1990) proposed reduce to standard linear mixed effects model estimators when  $f$  is linear and reduce to nonlinear least squares estimators if there is no random effects.

## 1.3 Software

The R package nlme (Pinheiro et al., 2017) can be used to fit user-specified nonlinear mixed effects model. This package uses (Lindstrom & Bates, 1990) method. It implemented a two-step iterative algorithm (Stegmann, Jacobucci,

Harring, & Grimm, 2018):

- Penalized nonlinear least squares step. The estimates for covariance matrix are fixed. The fixed effects and random effects estimates are updated.
- Linear mixed effect step. The estimates for covariance matrix are obtained by minimizing the log-likelihood of approximated distribution of  $\mathbf{y}$  using the current estimates for fixed and random effects.

NewtonRaphson algorithm converges more quickly than EM algorithm but the former is more sensitive to poor starting values (Stegmann et al., 2018). The nlme function utilizes the EM algorithm in the initial iteration in the linear mixed effect step and switches to NewtonRaphson algorithm afterwards.

## References

- Lindstrom, M. J., & Bates, D. M. (1990). Nonlinear mixed effects models for repeated measures data. *Biometrics*, 673–687.
- Pinheiro, J., Bates, D., DebRoy, S., Sarkar, D., Heisterkamp, S., Van Willigen, B., & Maintainer, R. (2017). Package nlme. *Linear and Nonlinear Mixed Effects Models, version*, 3–1.
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