Nonlinear mixed models

ForValueNet mixed and other models
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Bianca Eskelson

Nonlinear mixed-effects models

What are they and why use them?

- "Nonlinear mixed-effects (NLME) models are mixed-effects models in which some, or all, of the fixed and random effects occur nonlinearly in the model function (Pinheiro and Bates 2000, p. 306)."
  - Extension of linear mixed-effects (LME) models in which the conditional expectation of the response given the random effects is allowed to be a nonlinear function
  - Extension of nonlinear regression models for independent data in which random effects are incorporated in the coefficients to allow them to vary by group

LME vs. NLME

Why use NLME models instead of LME models?

- Interpretability, parsimony, and validity beyond the observed range of the data

Costs of using NLME instead of LME models:

- Marginal likelihood function has no closed-form expression
  → approximate likelihood function used for parameter estimation
  → estimation algorithms more computationally extensive
  → less reliable inference results
- Starting estimates for fixed-effects coefficients required

LME vs. NLME (cont'd)

Similarities of NLME and LME models:

- Both models used with grouped data
- Describe a response variable as a function of covariates, taking into account the correlation among observations in the same group
- Random effects used to represent within-group dependence
- Assumptions about random effects and within-group errors identical

NLS vs. NLME

- Nonlinear regression models with fixed effects only → nonlinear least squares (NLS)
- Using NLS instead of NLME for grouped data prevents us from understanding the true structure of the data and from considering different sources of variability that may be of interest in themselves.

Notation

For a single-level of grouping, the *j*th observation on the *i*th group is modeled as:

$$y_{ij} = f\left(\phi_{ij}, \upsilon_{ij}\right) + \varepsilon_{ij} \qquad i = 1,\ldots,M, \quad j = 1,\ldots,n_i$$

M is the number of groups

n_i is the number of observations on the *i*th group

$\varepsilon_{ij} \sim N\left(0, \sigma^2\right)$ is the within-group error

f is a general, real-valued, differentiable function of a group-specific parameter vector ϕ_{ij} and a covariate vector υ_{ij}; nonlinear in at least one component of ϕ_{ij}

Notation (cont'd)

ϕ_{ij} is modeled as:

$$\phi_{ij} = A_{ij}\beta + B_{ij}b_i \qquad b_i \sim N(0, \Psi)$$

β is a p-dimensional vector of fixed effects

b_i is a q-dimensional vector of random effects associated with the ith group with variance-covariance matrix Ψ

Matrices A_{ij} and B_{ij} are of appropriate dimensions and depend on the group and on the values of covariates at the jth observation.

Inference and Predictions

- *Inference* results based on the LME approximation to the log-likelihood function by Lindstrom and Bates (1990)
  - 'approximately asymptotic' → less reliable than the asymptotic inference results for LME models
- Compare nested NLME models through likelihood ratio tests
  - fit different nested models in which the random-effects structure changes and apply likelihood-ratio tests
- Information criterion statistics (e.g., AIC and BIC; 'the smaller the value the better the model') can be used to compare NLME models (nested and non-nested)
- Hypotheses about fixed effects should be tested using *t* and *F* tests
- *Predictions* for nlme models can be obtained at different levels of nesting or at the population level

Assumptions

- **Observations corresponding to different groups are independent**
- **Within-group errors are independent and identically distributed as and independent of the random effects**
  - Test assumption of equal variances with residual plots and normality assumption with normal probability plots for residuals
  - Remedies: variance-covariance structure of the within-group errors can be decomposed into two independent components: a variance structure and a correlation structure (for details see Pinheiro and Bates 2000, Chapter 5; Zuur et al. 2009, Chapters 4, 6, and 7)

Variance and correlation structures

- use variance functions available in nlme() to model within-group heteroscedasticity, e.g.,
  - fixed variance
  - different variances per stratum
  - power of covariate
  - exponential of covariate
- use correlation structures available nlme() in to represent the correlation structure of within-group errors, e.g.,
  - compound symmetry
  - general
  - autoregressive of order 1
  - continuous-time AR(1)
  - autoregressive-moving average

Assumptions (cont'd)

- **Random effects are normally distributed with mean zero and variance-covariance matrix Ψ**
  - Test assumption with normal probability plots for deviations of coefficients from average
- **Random effects corresponding to different groups are independent**

Model building strategies

- Starting values for fixed parameters required → finding values can be tedious
- Choose parameters that have meaningful graphical interpretations
- Take advantage of partially linear models
- Refine estimates of some parameters by iterating on them while holding all other parameters fixed
- Fit nonlinear fixed-effects model and use parameter estimates as starting values
- `selfStart` functions available for some common models

Which effects should be fixed and which should be random?

- Critical step: decide which coefficients need random effect to account for between-subject variation
- Boxplots of residuals by group → if residuals mostly negative for some groups and mostly positive for other groups, then include a random group effect

First possible modeling strategy:

start out with model that has random effects for all parameters

- convergence issues when the number of random effects is large relative to the number of groups
- assuming diagonal psi in model helps to avoid convergence problems
- Near-zero estimate for standard deviation of a random parameter → term could be dropped from model
- Use augmented prediction plots to determine whether NLME model can accommodate group effects

Second possible modeling strategy:

fit baseline model (minimum fixed and random effects)

- Add random effects
  - Include heteroscedastic variance structure
  - Correlation structure
  - Extra random effects (e.g., random slope)
- Once a reasonable model is found, add more fixed effects

Note: Fixed effects explain variation, random effects organize unexplained variation. Adding random effects adds information and improves diagnostic compatibility, but explains no more variation!

nlme() function in R

Typical call:

```
nlme(model, data, fixed, random, groups, start)
```

- `fixed` and `random` are formulas defining the structures of the fixed and random effects in the model
- By default, if `random` is omitted, all fixed effects in model are assumed to have associated random effect
- `start` → starting values for the fixed effects must be given
- default method is `method="ML"`
- **Note**: lme() default is method="REML"
- Some convergence error messages can be resolved by altering the `control` argument; see `?nlmeControl`