Nonlinear mixed Effects Model Fitting with nlme

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1 Motivation

Nonlinear mixed effect models combine the modeling techniques of nonlinear regression and mixed effects modeling. Nonlinear regression is applied, if there is a nonlinear model whose structure is known and which is belived to underpin the data. This implies that the number of parameters is fixed a priori and nonlinear regression is applied to estimate the parameter values.
Mixed-effects models can be applied if data is collected from different groups, whose parameter values might vary. Instead of modeling each group by itself, parameter variation is modeled by an underlying distribution. To combine these two approaches is conceptually quite natural.

2 The model

The model for single-level non-linear mixed effects can be formulated as follows:

$$y_{ij} = f(\boldsymbol{\phi}_{ij}, \boldsymbol{\nu}_{ij}) + \varepsilon_{ij} \quad i = 1, \ldots, M \quad j = 1, \ldots, n_i \tag{1}$$

where $\boldsymbol{\phi}_{ij}$ is an observation specific parameter vector. $\boldsymbol{\nu}_{ij}$ is a covariate vector and $\varepsilon_{ij} \sim \mathcal{N}_1(0, \sigma^2)$. M is the number of groups, and n_i the number of observations within a group. $\boldsymbol{\phi}_{ij}$ is modeled via

$$\boldsymbol{\phi}_i = \boldsymbol{A}_{ij}\boldsymbol{\beta} + \boldsymbol{B}_{ij}\boldsymbol{b}_i \quad \boldsymbol{b}_i \sim \mathcal{N}(0, \Psi), \quad \varepsilon_{ij} \perp \boldsymbol{b}_i \quad \forall i, j \tag{2}$$

Note that the matrices are dependent on each observation to allow for incorporation of covariate effects in the parameter model.

3 Starting Values

In nls- as well as in nlme-modeling one needs to supply some starting estimate of the parameter values. These can be either taken from literature, or estimated from the data itself. If the parameters have clear visual interpretation, they may be derived from the from the data directly via inspection. If the model is

linearizable or conditionally linearizable, a regression on the linearized model can be performed.
For many non-linear functions, that are often used, the nlme-package provides so-called selfstarting functions.

4 Introduction of Covariates

The variation in the population of parameters on the group level, might be in part explained by additional covariates. The potential incorporation of covariates into (2) is the reason, why the design matrices in (2) are allowed to change for individual observations. A plot of some estimated random effect versus the covariate values, will give an indication, if incorporation of a covariate in the fixed design matrix will lead to better fits. Since the incorporation of the covariate leads to a drop in unexplained variance for the parameter in question, often the random effect can be omitted. However, it is also possible, that the introduction of additional random effects is beneficial.

5 Extended nlme Models

As an extension to the above model, one can relax the condition, that the within-group errors ε_{ij} need to have constant variance and be uncorrelated. For the case of non-constant variance, a natural way to model this is:

$$\mathrm{Var}(\varepsilon|\boldsymbol{b}_i) = \sigma \times g^2(\mu_{ij}, \boldsymbol{\nu}_{ij}, \boldsymbol{\delta}), \quad i = 1, \dots, M, \quad j = 1, \dots, n_i \tag{3}$$

where $\mu_{ij} = \mathrm{E}[y_{ij}|\boldsymbol{b}_i]$, $\boldsymbol{\nu}_{ij}$ is a variance-covariate vector, $\boldsymbol{\delta}$ is a vector of variance parameters and $g(\cdot)$ is the variance function.
This allows to correct for trends that are observed for the within-group errors with respect to either covariates, or the fitted values. Note that in this formulation however, random effects and within-group errors are no longer independent. In nlme, commonly used variance functions are implemented in the varFunc-constructor functions.

6 Practical Model Fitting Procedure with nlme

To find a good Nonlinear mixed effect model requires expertise and should not be automatized! Nevertheless, there is a general procedure which usually leads to good results.

6.1 Data overview

Look at structure and plots of data to get a first impression. Check for outliers and plausibility of the model.
R-Commands:
`head, str, plot.nfnGroupedData`

6.2 Preliminary nls-fit

Fit a nonlinear regression, to check plausibility of model and see if the nls-model assumptions are actually violated (constant and independent errors).
R-Commands:
`nls, plot.nls`

6.3 nlsList-fit

Fit separate nls-models on each group level to get hints about covariance structure of random effects, particularly which random effects should be included in the model, and what the covariance structure should look like.
R-Commands:
`nlsList, intervals.lmList, pairs.lmList`

6.4 nlme-fit

Fit a series of nlme models with different random effects covariance structure. Pay atttention to over paramterization of covariance structure. Compare models with anova. Also, check introduction of additional covariates to explain variation in the parameter values.
R-Commands:
`nlme, update, anova.lme, intervals.lme, ranef`

6.5 Checking model fit and assumptions

Check if model assumptions are valid and, if not, check use of extended nonlinear mixed models.
R-Commands:
`plot.lme, qqnorm.lme, intervals.lme, augPred, plot.augPred`