Mixed-Effects Models in R

An Appendix to An R Companion to Applied Regression, Second Edition

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Abstract

Mixed-effects models are commonly employed in the analysis of grouped or clustered data, where observations in a cluster cannot reasonably be assumed to independent of one-another. In this appendix, we explain how to use the lme function in the nlme package and the lmer function in the lme4 package to fit linear mixed-effects models to hierarchical and longitudinal data. In the first instance, individuals are clustered into higher-level units (such as students within schools); in the second instance repeated observations are taken on individuals, who define the clusters. We also describe the use of the glmer function in the lme4 package for fitting generalized linear mixed-effects models, and the nlme function in the nlme package for fitting nonlinear mixed-effects models.

1 Introduction

The normal linear model is described in Fox and Weisberg (2011, Chapter 4). For the *i*th observation, i = 1, ..., n, the model is

$$y_i = \beta_1 x_{1i} + \beta_2 x_{2i} + \dots + \beta_p x_{pi} + \varepsilon_i$$

$$\varepsilon_i \sim \text{NID}(0, \sigma^2)$$

Here y_i is the response, x_{1i}, \ldots, x_{pi} are regressors for case *i* (Fox and Weisberg, 2011, Page 149), and β_1, \ldots, β_p are fixed and generally unknown parameters. In this appendix will will generally assume $x_{1i} = 1$, to accomodate an intercept. The only random variables on the right-hand side of this model are the statistical errors ε_i , and these random variables are specified as independent and normally distributed. We can think of the ε_i as providing a random effect, as without them the responses y_i would be completely determined by the xs. The distribution of the ε_i is fully determined by the value of σ^2 , which we can call the error variance component. As in Fox and Weisberg (2011, Chapter 4) the normality assumption is stronger than is needed to fit linear models with errors that are independent with constant variance, but we include the assumption here because normality or some other similar assumption is needed for fitting the more complex mixed models we discuss in this appendix.

For comparison with the linear mixed model of the next section, we rewrite the linear model in matrix form,

$$\mathbf{y} = \mathbf{X} \boldsymbol{eta} + \boldsymbol{\varepsilon} \ \boldsymbol{\varepsilon} \sim \mathbf{N}_n(\mathbf{0}, \sigma^2 \mathbf{I}_n)$$

where $\mathbf{y} = (y_1, y_2, ..., y_n)'$ is the response vector; \mathbf{X} is the model matrix, with typical row $\mathbf{x}'_i = (x_{1i}, x_{2i}, ..., x_{pi}); \boldsymbol{\beta} = (\beta_1, \beta_2, ..., \beta_p)'$ is the vector of regression coefficients; $\boldsymbol{\varepsilon} = (\varepsilon_1, \varepsilon_2, ..., \varepsilon_n)'$ is the

vector of errors; \mathbf{N}_n represents the *n*-variable multivariate-normal distribution; $\mathbf{0}$ is an $n \times 1$ vector of 0s; and \mathbf{I}_n is the order-*n* identity matrix.

Mixed-effect models, or just *mixed models*, include additional random-effect terms and associated variance and covariance components, and are often appropriate for representing clustered, and therefore dependent, data — arising, for example, when data are collected hierarchically, when observations are taken on related individuals such as siblings, or when data are gathered over time on the same individuals.

There are several packages in R for fitting mixed models to data, the most commonly used of which are the **nlme** (?Pinheiro et al., 2014) and **lme4** (Bates et al., 2014) packages, and which we discuss in this appendix.¹ The **nlme** package is a part of the standard R distribution, and the **lme4** package is available on CRAN.

Section 2 describes how to fit linear mixed models using **nlme** and **lme4**. Section 3 deals with generalized linear mixed models, fit by the **glmer** function in the **lme4** package, and Section 4 deals with nonlinear mixed models fit by the **nlme** function in the **nlme** package. Mixed models are a large and complex subject, and we will only scratch the surface here. Bayesian approaches, which we do not cover, are also common and are available in R: See the complementary readings in Section 5.

2 Linear Mixed Models

Linear mixed models (LMMs) may be expressed in different but equivalent forms. In the social and behavioral sciences, it is common to express such models in hierarchical form, as illustrated in Section 2.1. The lme (linear mixed effects) function in the nlme package and the lmer (linear mixed-effects regression, pronounced "elmer") function in the lme4 package, however, employ the Laird-Ware form of the LMM, after a seminal paper on the topic published by Laird and Ware (1982). We describe here only problems with a two-level hierarchy, such as students in schools, although more levels of hierarchy are possible (e.g., students within schools; schools within districts; districts within states; and so on). The model we describe extends to more levels but the subscripts needed get unwieldy. For i = 1, ..., M groups, we have

$$y_{ij} = \beta_1 x_{1ij} + \dots + \beta_p x_{pij}$$
(1)
+ $b_{i1} z_{1ij} + \dots + b_{iq} z_{qij} + \varepsilon_{ij}$
 $b_{ik} \sim N(0, \psi_k^2), Cov(b_{ik}, b_{ik'}) = \psi_{kk'}$
 $\varepsilon_{ij} \sim N(0, \sigma^2 \lambda_{ijj}), Cov(\varepsilon_{ij}, \varepsilon_{ij'}) = \sigma^2 \lambda_{ijj'}$

where

- y_{ij} is the value of the response variable for the *j*th of n_i observations in the *i*th of M groups or clusters.
- β_1, \ldots, β_p are the *fixed-effect coefficients*, which are identical for all groups.
- x_{1ij}, \ldots, x_{pij} are the fixed-effect regressors for observation j in group i; the first regressor is usually for the regression constant, $x_{1ij} = 1$.

¹nlme stands for nonlinear mixed effects, even though the package also includes the lme function for fitting *linear* mixed models. Similarly, **lme4** stands for linear mixed effects with S4 classes, but also includes functions for fitting generalized linear and nonlinear mixed models.

- b_{i1}, \ldots, b_{iq} are random effects for group *i*, assumed to have a multivariate normal distribution. The random effects are different in each group. The b_{ik} are thought of as random variables, not as parameters, and are similar in this respect to the errors ε_{ij} .
- z_{1ij}, \ldots, z_{qij} are the random-effect regressors. In many cases the zs are a subset of the xs and may include *all* of the xs.
- ψ_k^2 are the variances and $\psi_{kk'}$ the covariances among the random effects. The variances and covariances of the random effects are the same in each group. In some applications, the ψ_s are parametrized in terms of a relatively small number of fundamental parameters.
- ε_{ij} is the error for observation j in group i. The errors for group i are assumed to have a multivariate normal distribution.
- $\sigma^2 \lambda_{ijj'}$ is the covariance between errors ε_{ij} and $\varepsilon_{ij'}$ in group *i*. Generally, the $\lambda_{ijj'}$ are parametrized in terms of a few basic parameters, and their specific form depends upon context. For example, when observations are sampled independently within groups and are assumed to have constant error variance (as in the application developed in Section 2.1), $\lambda_{ijj} = 1$, $\lambda_{ijj'} = 0$ (for $j \neq j'$), and thus the only free parameter to estimate is the common error variance, σ^2 . The **Imer** function in the **Ime4** package handles only models of this form. In contrast, if the observations in a "group" represent longitudinal data on a single individual, then the structure of the λ s may be specified to capture autocorrelation among the errors, as is common in observations collected over time. The **Ime** function in the **nIme** package can handle autocorrelated and heteroscedastic errors (as in the application in Section 2.4, which employs autocorrelated errors).
- The random effects in different groups $i \neq i'$ are uncorrelated, so $\text{Cov}(b_{ik}, b_{i'k'}) = 0$ and $\text{Cov}(\varepsilon_{ij}, \varepsilon_{i'j'}) = 0$, even if j = j'.

The matrix form of this model is equivalent but considerably simpler to write down,

$$egin{array}{rcl} \mathbf{y}_i &=& \mathbf{X}_i oldsymbol{eta} + \mathbf{Z}_i \mathbf{b}_i + oldsymbol{arepsilon}_i \ \mathbf{b}_i &\sim& \mathbf{N}_q(\mathbf{0}, oldsymbol{\Psi}) \ oldsymbol{arepsilon}_i &\sim& \mathbf{N}_{n_i}(\mathbf{0}, \sigma^2 oldsymbol{\Lambda}_i) \end{array}$$

where

- \mathbf{y}_i is the $n_i \times 1$ response vector for observations in the *i*th group. The n_i need not all be equal.
- \mathbf{X}_i is the $n_i \times p$ model matrix of fixed-effect regressors for observations in group *i*.
- β is the $p \times 1$ vector of fixed-effect coefficients, invariant across groups.
- \mathbf{Z}_i is the $n_i \times q$ matrix of regressors for the random effects for observations in group *i*.
- \mathbf{b}_i is the $q \times 1$ vector of random effects for group *i*, potentially different in different groups.
- ε_i is the $n_i \times 1$ vector of errors for observations in group *i*.
- Ψ is the $q \times q$ covariance matrix for the random effects. To conform with previous notation, the diagonal elements are $\psi_{jj} = \psi_j^2$ and the off-diagonals are $\psi_{jj'}$.

• $\sigma^2 \Lambda_i$ is the $n_i \times n_i$ covariance matrix for the errors in group *i*; for the lmer function the error covariance matrix for group *i* is $\sigma^2 \mathbf{I}_{n_i}$. Models with other specifications for Λ_i can be fit with the lme function in the nlme package at the cost of increased complexity, both of specifying a model and of computations.

2.1 An Illustrative Application to Hierarchical Data

Applications of mixed models to hierarchical data have become common in the social sciences, and nowhere more so than in research on education. The following example is borrowed from Raudenbush and Bryk's influential text on hierarchical linear models (Raudenbush and Bryk, 2002), and also appears in a paper by Singer (1998), which shows how such models can be fit by the MIXED procedure in SAS. In this section, we will show how to model Raudenbush and Bryk's data using the lme function in the nlme package and the lmer function in the lme4 package.

The data for the example, from the 1982 "High School and Beyond" survey, are for 7185 highschool students from 160 schools. There are, therefore, on average $7185/160 \approx 45$ students per school. We have two levels of hierarchy, with schools at the first or group level, and students within schools as the second (individual) level of hierarchy. The data are conveniently available in the data frames MathAchieve and MathAchSchool in the nlme package:² The first data frame pertains to students within schools, with one row in the data frame for each of the 7185 students. Here are the first 10 rows of this data set, all for students in school number 1224:

```
> library(nlme)
```

```
> head(MathAchieve, 10) # first 10 students
```

```
Grouped Data: MathAch ~ SES | School
```

	${\tt School}$	Minority	Sex	SES	${\tt MathAch}$	MEANSES
1	1224	No	Female	-1.528	5.876	-0.428
2	1224	No	Female	-0.588	19.708	-0.428
3	1224	No	Male	-0.528	20.349	-0.428
4	1224	No	Male	-0.668	8.781	-0.428
5	1224	No	Male	-0.158	17.898	-0.428
6	1224	No	Male	0.022	4.583	-0.428
7	1224	No	Female	-0.618	-2.832	-0.428
8	1224	No	Male	-0.998	0.523	-0.428
9	1224	No	Female	-0.888	1.527	-0.428
10	1224	No	Male	-0.458	21.521	-0.428

> dim(MathAchieve)

[1] 7185 6

The second data frame pertains to the schools into which students are clustered, and there is one row for each of the M = 160 schools. The first 10 schools are:

> head(MathAchSchool, 10) # first 10 schools

²Data sets in the **nlme** package are actually *grouped-data objects*, which behave like data frames but include extra information that is useful when using functions from **nlme**. The extra features of grouped-data objects are not used by the **lme4** functions. We will mostly ignore the extra features, apart from a brief discussion later in this appendix.

	${\tt School}$	Size	Sector	PRACAD	DISCLIM	HIMINTY	MEANSES
1224	1224	842	Public	0.35	1.597	0	-0.428
1288	1288	1855	Public	0.27	0.174	0	0.128
1296	1296	1719	Public	0.32	-0.137	1	-0.420
1308	1308	716	Catholic	0.96	-0.622	0	0.534
1317	1317	455	Catholic	0.95	-1.694	1	0.351
1358	1358	1430	Public	0.25	1.535	0	-0.014
1374	1374	2400	Public	0.50	2.016	0	-0.007
1433	1433	899	Catholic	0.96	-0.321	0	0.718
1436	1436	185	Catholic	1.00	-1.141	0	0.569
1461	1461	1672	Public	0.78	2.096	0	0.683

> dim(MathAchSchool)

[1] 160 7

In the analysis that follows, we will use the following variables:

- School: an identification number for the student's school that appears in both MathAchieve and MathAchSchool. Although it is not required by lme or lmer, students in a specific school are in consecutive rows of the MathAchieve data frame, a convenient form of data organization. The schools define groups or clusters: It is unreasonable to suppose that students in the same school are independent of one another because, for example, they have the same teachers, textbooks, and general school environment.
- SES: the socioeconomic status of the student's family, centered to an overall mean of 0 (within rounding error). This is a student-level variable from the MathAch data frame, sometimes called an *inner* or *individual-level* variable.
- MathAch: the student's score on a math-achievement test, a student-level variable.
- Sector: a factor coded "Catholic" or "Public". This is a school-level variable and hence is identical for all students in the same school. A variable of this kind is sometimes called an *outer variable* or a *contextual variable*. Because the Sector variable resides in the school data set, we need to copy it over to the appropriate rows of the student data set. Such data-management tasks are common in preparing data for mixed-modeling.³
- MEANSES: another outer variable, giving the mean SES for students in each school; we call outer variables that aggregate individual-level data to the group level *compositional variables*.

This variable appears in both data sets, but it seems to have been calculated incorrectly because its values in MathAchSchool are slightly different from the school means computed directly from the MathAchieve data set. We will therefore recompute it using the tapply function (see Fox and Weisberg, 2011, Section 8.4).⁴

³This data-management task is implied by the Laird-Ware form of the LMM. Some software that is specifically oriented towards modeling hierarchical data employs two data sets — one for contextual variables and one for individual-level variables — corresponding respectively to the MathAchieveSchool and MathAchieve data sets in the present example.

⁴We are not sure why the school means given in the MathAchieveSchool and MathAchieve data sets differ from the values that we compute directly. It is possible that the values in these data sets were computed from larger populations of students in the sampled schools.

> mses <- with(MathAchieve, tapply(SES, School, mean))</pre>

To decode this complex command, the with function tells R to do computions using the Math-Achieve data. The tapply function applies the mean function to the variable SES, with a separate mean for each value of School. The result is stored in the new variable mses, and it will consist of the mean SES for each of the 160 schools; here are the first 8:

> mses[as.character(MathAchSchool\$School[1:8])] # for first 8 schools

1224 1288 1296 1308 1317 1358 1374 1433 -0.43438 0.12160 -0.42550 0.52800 0.34533 -0.01967 -0.01264 0.71200

The integers shown—for example, 1224–are the school ID numbers.

Because the student-level and school-level variables are in different data frames, we will create a new data frame that includes both of these, because this is the format that the R functions we use expect. We name the new data frame **Bryk**, and start by copying the student-level data we want:

```
> Bryk <- as.data.frame(MathAchieve[, c("School", "SES", "MathAch")])
> names(Bryk) <- tolower(names(Bryk))</pre>
```

Using as.data.frame, we make Bryk an ordinary data frame rather than a grouped-data object. We rename the variables to lower-case in conformity with our usual practice — data frames start with upper-case letters, variables with lower-case letters. Here are 20 randomly selected rows of this data set:

```
> set.seed(12345) # for reproducibility
> (sample20 <- sort(sample(nrow(Bryk), 20))) # 20 randomly sampled students</pre>
```

[1] 9 248 1094 1195 1283 2334 2783 2806 2886 3278 3317 3656 5180 5223 5278 [16] 5467 6292 6365 6820 7103

> Bryk[sample20,]

school ses mathach 9 1224 -0.888 1.527 248 1433 1.332 18.496 1094 2467 0.062 6.415 1195 2629 0.942 11.437 1283 2639 -1.088 -0.7632334 3657 -0.288 13.156 2783 0.792 4042 14.500 2806 4042 0.482 3.687 2886 4223 1.242 20.375 3278 4511 -0.178 15.550 3317 4511 0.342 7.447 3656 5404 0.902 18.802 5180 7232 0.442 23.591 5223 7276 -1.098 -1.5255278 7332 -0.508 16.114 54677364-0.17820.32562928707-0.22818.46363658800-0.65811.92868209198-0.5382.349710395500.7524.285

Next, we add the outer variables to the data frame, in the process computing a version of SES, called cses, that is centered at the school means:

```
> sector <- MathAchSchool$Sector
> names(sector) <- row.names(MathAchSchool)
> Bryk <- within(Bryk,{
+ meanses <- as.vector(mses[as.character(school)])
+ cses <- ses - meanses
+ sector <- sector[as.character(school)]
+ })
> Bryk[sample20, ]
```

	school	ses	mathach	sector	cses	meanses
9	1224	-0.888	1.527	Public	-0.45362	-0.43438
248	1433	1.332	18.496	Catholic	0.62000	0.71200
1094	2467	0.062	6.415	Public	0.39173	-0.32973
1195	2629	0.942	11.437	Catholic	1.07965	-0.13765
1283	2639	-1.088	-0.763	Public	-0.12357	-0.96443
2334	3657	-0.288	13.156	Public	0.36118	-0.64918
2783	4042	0.792	14.500	Catholic	0.39000	0.40200
2806	4042	0.482	3.687	Catholic	0.08000	0.40200
2886	4223	1.242	20.375	Catholic	1.33600	-0.09400
3278	4511	-0.178	15.550	Catholic	-0.07086	-0.10714
3317	4511	0.342	7.447	Catholic	0.44914	-0.10714
3656	5404	0.902	18.802	Catholic	0.07702	0.82498
5180	7232	0.442	23.591	Public	0.53212	-0.09012
5223	7276	-1.098	-1.525	Public	-1.17623	0.07823
5278	7332	-0.508	16.114	Catholic	-0.80500	0.29700
5467	7364	-0.178	20.325	Catholic	-0.08864	-0.08936
6292	8707	-0.228	18.463	Public	-0.38313	0.15513
6365	8800	-0.658	11.928	Catholic	0.05125	-0.70925
6820	9198	-0.538	2.349	Catholic	-1.03000	0.49200
7103	9550	0.752	4.285	Public	0.69897	0.05303

These steps are a bit tricky:

- The students' school numbers (in school) are converted to character values, used to index the outer variables in the school dataset. This procedure assigns the appropriate values of meanses and sector to each student.
- To make this indexing work for the Sector variable in the school data set, the variable is assigned to the global vector sector, whose names are then set to the row names of the school data frame.

Following Raudenbush and Bryk, we will ask whether students' math achievement is related to their socioeconomic status; whether this relationship varies systematically by sector; and whether the relationship varies randomly across schools within the same sector.

2.1.1 Examining the Data

As in all data analysis, it is advisable to examine the data before embarking upon statistical modeling. There are too many schools to look at each individually, so we start by selecting samples of 20 public and 20 Catholic schools, storing each sample in a data frame:

```
> cat <- with(Bryk, sample(unique(school[sector == "Catholic"]), 20))
> Cat.20 <- Bryk[is.element(Bryk$school, cat), ]
> dim(Cat.20)
[1] 1027 6
> pub <- with(Bryk, sample(unique(school[sector == "Public"]), 20))
> Pub.20 <- Bryk[is.element(Bryk$school, pub), ]
> dim(Pub.20)
```

```
[1] 739 6
```

Thus Cat.20 contains the data for 20 randomly selected Catholic schools, and Pub.20 the data for 20 randomly selected public schools.

We use Lattice graphics provided by the **lattice** package (see Fox and Weisberg, 2011, Section 7.3.1) to visualize the relationship between math achievement and school-centered SES in the sampled schools:

```
> library(lattice) # for Lattice graphics
> trellis.device(color=FALSE) # to get black-and-white figures
> xyplot(mathach ~ cses | school, data=Cat.20, main="Catholic",
+ type=c("p", "r", "smooth"), span=1)
> xyplot(mathach ~ cses | school, data=Pub.20, main="Public",
+ type=c("p", "r", "smooth"), span=1)
```

The call to trellis.device creates a graphics-device window appropriately set up for Lattice graphics, but with non-default options. In this case, we specified monochrome graphics (color = FALSE) so that this appendix will print well in black-and-white; the default is to use color. The xyplot function draws a Lattice display of scatterplots of math achievement against socioeconomic status, one scatterplot for each school, as specified by the formula mathach ~ cses | school. The school number appears in the strip label above each plot. We created one graph for Catholic schools (Figure 1) and another for public schools (Figure 2). The argument main to xyplot supplies the title of each graph. Each cell or *panel* of the display uses data from only one school. The argument type=c("p", "r", "smooth") specifies plotting points, the OLS regression line, and a loess smooth; see the argument type on the help page for panel.xyplot. Because of the small number of students in each school, we set the span for the loess smoother to 1.

Examining the scatterplots in Figures 1 and 2, there is a weak positive relationship between math achievement and SES in most Catholic schools, although there is variation among schools: In some schools the slope of the regression line is near 0 or even negative. There is also a positive relationship between the two variables for most of the public schools, and here the average slope is



Catholic

Figure 1: Trellis display of math achievement by socio-economic status for 20 randomly selected Catholic schools. The broken lines give linear least-squares fits, the solid lines local-regression fits.



Figure 2: Trellis display of math achievement by socio-economic status for 20 randomly selected public schools.

Public

larger. Considering the moderate number of students in each school, linear regressions appear to provide a reasonable summary of the within-school relationships between math achievement and SES.

2.1.2 Using lmList to Fit Regressions Separately to Each School

The **nlme** package includes the function **lmList** for fitting a linear model to the observations in each group, returning a list of linear-model objects, which is itself an object of class "**lmList**".⁵ Here, we fit the regression of math-achievement scores on centered socioeconomic status for each school, creating separate "**lmList**" objects for Catholic and public schools:

```
> cat.list <- lmList(mathach ~ cses | school, subset = sector=="Catholic",
+ data=Bryk)
> pub.list <- lmList(mathach ~ cses | school, subset = sector=="Public",
+ data=Bryk)
```

Several methods exist for manipulating "lmList" objects. For example, the generic intervals function has a method for objects of this class that returns by default 95-percent confidence intervals for the regression coefficients; the confidence intervals can be plotted, as follows:

```
> plot(intervals(cat.list), main="Catholic")
```

```
> plot(intervals(pub.list), main="Public")
```

The resulting graphs are shown in Figures 3 and 4. In interpreting these graphs, we need to be careful to take into account that we have not constrained the scales for the plots to be the same, and indeed the scales for the intercepts and slopes in the public schools are wider than in the Catholic schools. Because the SES variable is centered to 0 within schools, the intercepts are interpretable as the average level of math achievement in each school. It is clear that there is substantial variation in the intercepts among both Catholic and public schools; the confidence intervals for the slopes, in contrast, overlap to a much greater extent, but there is still apparent school-to-school variation.

Parallel boxplots provide a different visualization of the estimated intercepts and slopes that is easier to summarize. First, we save the coefficient estimates:

```
> cat.coef <- coef(cat.list)</pre>
> head(cat.coef, 6)
     (Intercept)
                      cses
7172
            8.067
                   0.9945
4868
           12.310 1.2865
2305
           11.138 -0.7821
8800
            7.336
                   2.5681
                   1.6035
5192
           10.409
4523
            8.352
                   2.3808
> pub.coef <- coef(pub.list)</pre>
> head(pub.coef, 6)
```

⁵A similar function is included in the **lme4** package.



Catholic

Figure 3: 95-percent confidence intervals for the intercepts and slopes of the within-schools regressions of math achievement on centered SES, for Catholic schools.



Public

Figure 4: 95-percent confidence intervals for the intercepts and slopes of the within-schools regressions of math achievement on centered SES, for public schools.



Figure 5: Boxplots of intercepts and slopes for the regressions of math achievement on centered SES in Catholic and public schools.

	(Intercept)	cses
8367	4.553	0.2504
8854	4.240	1.9388
4458	5.811	1.1318
5762	4.325	-1.0141
6990	5.977	0.9477
5815	7.271	3.0180

The calls to **coef** extract matrices of regression coefficients from the **lmList** objects, with rows representing schools. Then, we draws separate plots for the intercepts and for the slopes:

```
> old <- par(mfrow=c(1, 2))
> boxplot(cat.coef[, 1], pub.coef[, 1], main="Intercepts",
+    names=c("Catholic", "Public"))
> boxplot(cat.coef[, 2], pub.coef[, 2], main="Slopes",
+    names=c("Catholic", "Public"))
> par(old) # restore
```

Setting the plotting parameter mfrow to 1 row and 2 columns produces the side-by-side pairs of boxplots in Figure 5; mfrow is then returned to its previous value. The Catholic schools have a higher average level of math achievement than the public schools, while the average slope relating math achievement to SES is larger in the public schools than in the Catholic schools.

2.1.3 Fitting a Hierarchical Linear Model with lme

Following Raudenbush and Bryk (2002) and Singer (1998), we will fit a hierarchical linear model to the math-achievement data. This model consists of two sets of equations: First, within schools,

we have the regression of math achievement on the individual-level covariate SES; it aids interpretability of the regression coefficients to center SES at the school average; then the intercept for each school estimates the average level of math achievement in the school. Using centered SES, the individual-level equation for individual j in school i is

$$\mathrm{mathach}_{ij} = \alpha_{0i} + \alpha_{1i} \mathrm{cses}_{ij} + \varepsilon_{ij} \tag{2}$$

Second, at the school level, and also following Raudenbush, Bryk, and Singer, we will entertain the possibility that the school intercepts and slopes depend upon sector and upon the average level of SES in the schools:

$$\alpha_{0i} = \gamma_{00} + \gamma_{01} \operatorname{meanses}_i + \gamma_{02} \operatorname{sector}_i + u_{0i}$$

$$\alpha_{1i} = \gamma_{10} + \gamma_{11} \operatorname{meanses}_i + \gamma_{12} \operatorname{sector}_i + u_{1i}$$
(3)

This kind of formulation is sometimes called a *coefficients-as-outcomes* model.⁶

Substituting the school-level Equations 3 into the individual-level Equation 2 produces

 $\begin{aligned} \text{mathach}_{ij} &= \gamma_{00} + \gamma_{01} \text{meanses}_i + \gamma_{02} \text{sector}_i + u_{0i} \\ &+ (\gamma_{10} + \gamma_{11} \text{meanses}_i + \gamma_{12} \text{sector}_i + u_{1j}) \text{cses}_{ij} + \varepsilon_{ij} \end{aligned}$

Rearranging terms,

$$\begin{aligned} \text{mathach}_{ij} &= \gamma_{00} + \gamma_{01} \text{meanses}_i + \gamma_{02} \text{sector}_i + \gamma_{10} \text{cses}_{ij} \\ &+ \gamma_{11} \text{meanses}_i \text{cses}_{ij} + \gamma_{12} \text{sector}_i \text{cses}_{ij} \\ &+ u_{0i} + u_{1i} \text{cses}_{ij} + \varepsilon_{ij} \end{aligned}$$

Here, the γ s are fixed effect coefficients, while the us (and the individual-level errors ε_{ij}) are random effects.

Finally, rewriting the model in the notation of the LMM (Equation 1),

$$mathach_{ij} = \beta_1 + \beta_2 meanses_i + \beta_3 sector_i + \beta_4 cses_{ij}$$
(4)
+ $\beta_5 meanses_i cses_{ij} + \beta_6 sector_i cses_{ij}$
+ $b_{i1} + b_{i2} cses_{ij} + \varepsilon_{ij}$

The change is purely notational, using β s for fixed effects and bs for random effects. (In the data set, however, the school-level variables — that is, meanses and sector — are attached to the observations for the individual students, as previously described.) We place no constraints on the covariance matrix of the random effects⁷, so

$$\Psi = V \begin{bmatrix} b_{i1} \\ b_{i2} \end{bmatrix} = \begin{bmatrix} \psi_1^2 & \psi_{12} \\ \psi_{12} & \psi_2^2 \end{bmatrix}$$
(5)

Also the individual-level errors are independent within schools, with constant variance:

$$V(\boldsymbol{\varepsilon}_i) = \sigma^2 \mathbf{I}_{n_i}$$

⁶This coefficients-as-outcomes model assumes that the regressions of the within-school intercepts and slopes on school mean SES are linear. We invite the reader to examine this assumption by creating scatterplots of the within-school regression coefficients for Catholic and public schools, computed in the previous section, against school mean SES, modifying the hierarchical model in light of these graphs if the relationships appear nonlinear. For an analysis along these lines, see the discussion of the High School and Beyond data in Fox (2016, Chap. 23).

⁷We are assuming, however, that the random effects for group i are independent of the random effects for any other group i'.

Even though the individual-level errors are assumed to be independent, observations in the same school are correlated,

$$\operatorname{Var}(\operatorname{mathach}_{ij}) = \sigma^2 + \psi_1^2 + \operatorname{cses}_{ij}^2 \psi_2^2 + 2\operatorname{cses}_{ij} \psi_{12}$$
$$\operatorname{Cov}(\operatorname{mathach}_{ij}, \operatorname{mathach}_{ij'}) = \psi_1^2 + \operatorname{cses}_{ij} \operatorname{cses}_{ij'} \psi_2^2 + (\operatorname{cses}_{ij} + \operatorname{cses}_{ij'})\phi_{12}$$

while observations in different groups are uncorrelated.

As mentioned in Section 2, LMMs are fit with the lme function in the nlme package. Specifying the fixed effects in the call to lme is identical to specifying a linear model in a call to lm (see Chapter 4 of the text). Random effects are specified via the random argument to lme, which takes a one-sided model formula.

Before fitting a mixed model to the math-achievement data, we reorder the levels of the factor **sector** so that the contrast for **sector** will use the value 0 for the public sector and 1 for the Catholic sector, in conformity with the coding employed by Raudenbush and Bryk (2002) and by Singer (1998):⁸

```
> Bryk$sector <- factor(Bryk$sector, levels=c("Public", "Catholic"))
> contrasts(Bryk$sector)
```

Catholic Public 0 Catholic 1

Having established the contrast-coding for sector, the LMM in Equation 4 is fit as follows:

```
> bryk.lme.1 <- lme(mathach ~ meanses*cses + sector*cses,
+ random = ~ cses | school,
+ data=Bryk)
```

The formula for the random effects includes only the term for centered SES. As in a linear-model formula, a random intercept is implied unless it is explicitly excluded (by specifying -1 in the random formula). By default, 1me fits the model by *restricted maximum likelihood* (*REML*), which in effect corrects the maximum-likelihood estimator for degrees of freedom (see the complementary readings in Section 5).

```
> summary(bryk.lme.1)
```

```
Linear mixed-effects model fit by REML
Data: Bryk
   AIC BIC logLik
   46524 46592 -23252
Random effects:
Formula: ~cses | school
Structure: General positive-definite, Log-Cholesky parametrization
        StdDev Corr
(Intercept) 1.5426 (Intr)
```

 $^{{}^{8}}$ Recoding changes the values of the fixed effects coefficient estimates but does not change other aspects of the fitted model.

cses 0.3182 0.391 Residual 6.0598

Fixed effects: mathach ~ meanses * cses + sector * cses Value Std.Error DF t-value p-value 60.86 (Intercept) 12.128 0.1993 7022 0.0000 5.333 0.3692 157 14.45 0.0000 meanses 2.945 0.1556 7022 18.93 cses 0.0000 sectorCatholic 1.227 0.3063 157 4.00 0.0001 1.039 0.2989 7022 0.0005 meanses:cses 3.48 cses:sectorCatholic -1.643 0.2398 7022 -6.85 0.0000 Correlation: (Intr) meanss cses sctrCt mnss:c meanses 0.256 0.075 0.019 cses sectorCatholic -0.699 -0.356 -0.053 0.074 0.293 -0.026 meanses:cses 0.019 cses:sectorCatholic -0.052 -0.027 -0.696 0.077 -0.351 Standardized Within-Group Residuals: Min Q1 Med QЗ Max -3.15926 -0.72319 0.01705 0.75445 2.95822

Number of Observations: 7185 Number of Groups: 160

The output from the summary method for lme objects consists of several panels:

- The first panel gives the AIC (Akaike information criterion) and BIC (Bayesian information criterion), which can be used for model selection (Fox and Weisberg, 2011, Section 4.5), along with the log of the maximized restricted likelihood.
- The next panel displays estimates of the variance and covariance parameters for the random effects, in the form of standard deviations and correlations. Thus, $\hat{\psi}_1 = 1.543$, $\hat{\psi}_2 = 0.318$, $\hat{\sigma} = 6.060$, and $\hat{\psi}_{12} = 0.391 \times 1.543 \times 0.318 = 0.192$. The term labelled **Residual** is the estimate of σ .
- The table of fixed effects is similar to output from lm; to interpret the coefficients in this table, refer to the hierarchical form of the model given in Equations 2 and 3, and to the Laird-Ware form of the LMM in Equation 4 (which orders the coefficients differently from the lme output). In particular, the fixed-effect intercept coefficient $\hat{\beta}_1 = 12.128$ represents an estimate of the average level of math achievement in public schools, which are the baseline category for the dummy regressor for sector. The remaining coefficient estimates could be interpreted similarly to coefficients in a linear model. In particular, the apparent significance of the interaction terms suggests that main effect terms should not be interpreted without considering the interactions. We prefer to do this interpretation using the effects plots that we will introduce shortly.
- The panel labelled Correlation gives the estimated sampling correlations among the fixedeffect coefficient estimates. These coefficient correlations are not usually of direct interest.

Very large correlations, however, are indicative of an ill-conditioned model — the analog of high collinearity in a linear model.

• Some information about the standardized within-group residuals $(\hat{\varepsilon}_{ij}/\hat{\sigma})$, the number of observations, and the number of groups, appears at the end of the output.

The model we fit assumes that each school has its own slope and intercept sampled from a bivariate normal distribution with covariance matrix Ψ given by Equation 5 (page 15). Testing if the elements of Ψ are 0 can be of interest in some problems. We can test hypotheses about the variances and covariances of random effects by deleting random-effects terms from the model. Tests are based on the change in the log of the maximized restricted likelihood, calculating log likelihood-ratio statistics. When LMMs are fit by REML, we must be careful, however, to compare models that are identical in their fixed effects.

For the current illustration, we may proceed as follows:

```
> bryk.lme.2 <- update(bryk.lme.1,</pre>
      random = ~ 1 | school) # omitting random effect of cses
> anova(bryk.lme.1, bryk.lme.2)
           Model df
                             BIC logLik
                                           Test L.Ratio p-value
                       AIC
                1 10 46524 46592 -23252
bryk.lme.1
bryk.lme.2
               2
                  8 46521 46576 -23252 1 vs 2
                                                   1.124
                                                            0.57
> bryk.lme.3 <- update(bryk.lme.1,</pre>
      random = \ cses - 1 \ | \ school)
                                      # omitting random intercept
+
> anova(bryk.lme.1, bryk.lme.3)
           Model df
                             BIC logLik
                                           Test L.Ratio p-value
                       AIC
bryk.lme.1
                1 10 46524 46592 -23252
                  8 46740 46795 -23362 1 vs 2
                                                   220.6 <.0001
bryk.lme.3
                2
```

Each of these likelihood-ratio tests is on 2 degrees of freedom, because excluding one of the random effects removes not only its variance from the model but also its covariance with the other random effect. The large *p*-value in the first of these tests suggests no evidence of the need for a random slope for centered SES, or equivalently that $\psi_{12} = \psi_2^2 = 0$. The small *p*-value for the second test suggests that $\psi_1^2 \neq 0$, and even accounting for differences due to sector and mean school SES, the average math achievement varies from school to school.

A more careful formulation of these tests takes account of the fact that each null hypothesis places a variance (but not covariance) component on a boundary of the parameter space. Consequently, the null distribution of the LR test statistic is not simply chisquare with 2 degrees of freedom, but rather a mixture of chisquare distributions.⁹ Moreover, it is reasonably simple to compute the corrected p-value:

```
> pvalCorrected <- function(chisq, df){
+ (pchisq(chisq, df, lower.tail=FALSE) +
+ pchisq(chisq, df - 1, lower.tail=FALSE))/2
+ }
> pvalCorrected(1.124, df=2)
```

⁹See the complementary readings in Section 5 for discussion of this point.

[1] 0.4296

> pvalCorrected(220.6, df=2)

[1] 6.59e-49

Here, therefore, the corrected *p*-values are similar to the uncorrected ones.

Model bryk.lme.2, fit above, omits the non-significant random effects for cses; the resulting fixed-effects estimates are nearly identical to those for the initial model bryk.lme.1, which includes these random effects:

```
> summary(bryk.lme.2)
Linear mixed-effects model fit by REML
Data: Bryk
   AIC
          BIC logLik
 46521 46576 -23252
Random effects:
 Formula: ~1 | school
        (Intercept) Residual
StdDev:
              1.541
                       6.064
Fixed effects: mathach ~ meanses * cses + sector * cses
                     Value Std.Error
                                       DF t-value p-value
(Intercept)
                    12.128
                              0.1992 7022
                                            60.88 0.0000
meanses
                     5.337
                              0.3690 157
                                            14.46 0.0000
cses
                     2.942
                              0.1512 7022
                                            19.46 0.0000
sectorCatholic
                     1.225
                              0.3061 157
                                             4.00 0.0001
                              0.2910 7022
meanses:cses
                     1.044
                                             3.59 0.0003
cses:sectorCatholic -1.642
                              0.2331 7022
                                            -7.05 0.0000
 Correlation:
                    (Intr) meanss cses
                                         sctrCt mnss:c
                     0.256
meanses
                     0.000 0.000
cses
sectorCatholic
                    -0.699 -0.356 0.000
                     0.000 0.000 0.295
                                          0.000
meanses:cses
cses:sectorCatholic 0.000 0.000 -0.696
                                         0.000 -0.351
Standardized Within-Group Residuals:
    Min
               Q1
                       Med
                                 QЗ
                                         Max
-3.17012 -0.72488 0.01485 0.75424 2.96551
Number of Observations: 7185
Number of Groups: 160
```

This model is sufficiently simple, despite the interactions, to interpret the fixed effects from the estimated coefficients, but even here it is likely easier to visualize the model in effect plots (as discussed for linear models in Fox and Weisberg, 2011, Section 4.3.3). Our effects package has



Figure 6: Effect displays for the high-order terms in the LMM fit to the High School and Beyond data, bryk.lme.2.

methods for mixed models fit by functions in the **nlme** and **lme4** packages. In the present example, we can use the **allEffects** function to graph the high-order fixed effects in the LMM we fit to the High School and Beyond Data – that is, the interactions between mean and centered SES and between mean SES and sector – producing Figure 6:

> library(effects) > plot(allEffects(bryk.lme.2), rug=FALSE)

It is clear from these graphs that the impact of a student's SES on math achievement rises as the mean level of math achievement in his or her school rises, and is larger in public schools than in Catholic schools.

2.1.4 Fitting a Hierarchical Linear Model with 1mer

We can perform the same analysis employing lmer in the lme4 package. For example, to fit the initial hiearchical model considered in the previous section:

REML criterion at convergence: 46504 Scaled residuals: Min 10 Median 30 Max -3.159 -0.723 0.017 0.754 2.958 Random effects: Groups Variance Std.Dev. Corr Name school 2.380 1.543 (Intercept) 0.318 cses 0.101 0.39 Residual 36.721 6.060 Number of obs: 7185, groups: school, 160 Fixed effects: Estimate Std. Error t value 0.199 60.9 (Intercept) 12.128 5.333 0.369 14.4 meanses cses 2.945 0.156 18.9 sectorCatholic 1.227 0.306 4.0 0.299 3.5 meanses:cses 1.039 cses:sectorCatholic -1.6430.240 -6.9Correlation of Fixed Effects: (Intr) meanss cses sctrCt mnss:c meanses 0.256 cses 0.075 0.019 sectorCthlc -0.699 -0.356 -0.053 meanses:css 0.019 0.074 0.293 -0.026 css:sctrCth -0.052 -0.027 -0.696 0.077 -0.351

The estimates of the fixed effects and variance/covariance components are the same as those obtained from lme (see page 16), but the specification of the model is slightly different: Rather than using a random argument as in lme, the random effects in lmer are given directly in the model formula, enclosed in parentheses; as in lme, a random intercept is implied if it is not explicitly removed. An important difference between lme and lmer, however, is that lmer can accommodate *crossed* random effects, while lme cannot: Suppose, for example, that we were interested in teacher effects on students' achievement. Each student in a high school has several teachers, and so students would not be strictly nested within teachers.

A subtle difference between the lme and lmer output is that the former includes *p*-values for the Wald *t*-tests of the estimated coefficients while the latter does not. The *p*-values in lmer are suppressed because the Wald tests can be inaccurate. We address this issue in Section 2.2.

As in the previous section, let us proceed to remove the random slopes from the model, comparing the resulting model to the initial model by a likelihood-ratio text:

```
> bryk.lmer.2 <- lmer(mathach ~ meanses*cses + sector*cses + (1 | school),
+ data=Bryk)
```

```
> anova(bryk.lmer.1, bryk.lmer.2)
```

Out of an abundance of caution, **anova** refits the models using ML rather than REML, because LR tests of models fit by REML that differ in their *fixed* effects are inappropriate. In our case, however, the models compared have identical fixed effects and differ only in the *random* effects. A likelihood-ratio test is therefore appropriate even if the models are fit by REML. We can obtain this test by specifying the argument refit=FALSE:

The results are identical to those using lme.

2.2 Wald Tests for Linear Mixed Models

As we mentioned, it is inappropriate to perform likelihood-ratio tests for fixed effects when a LMM is fit by REML. Though it is sometimes recommended that ML be used instead to obtain LR tests of fixed effects, ML estimates can be substantially biased when there are relatively few higher-level units. Wald tests can be performed, however, for the fixed effects in a LMM estimated by REML, but as we also mentioned, Wald tests obtained for individual coefficients by dividing estimated fixed effects by their standard errors can be inaccurate. The same is true of more complex Wald tests on several degrees of freedom — for example, F-tests for terms in a linear mixed model.

One approach to obtaining more accurate inferences in LMMs fit by REML is to adjust the estimated covariance matrix of the fixed effects to reduce the typically downward bias of the coefficient standard errors, as suggested by Kenward and Roger (1997), and to adjust degrees of freedom for t and F tests (applying a method introduced by Satterthwaite, 1946). These adjustments are available for linear mixed models fit by lmer in the Anova and linearHypothesis functions in the **car** package, employing infrastructure from the **pbkrtest** package. For example,

```
> library(car)
> Anova(bryk.lmer.2, test="F")
```

Analysis of Deviance Table (Type II Wald F tests with Kenward-Roger df)

Response: mathach

F Df Df.res Pr(>F)

meanses	209.2	1	156	< 2e-16
cses	409.4	1	7023	< 2e-16
sector	16.0	1	154	9.8e-05
meanses:cses	12.9	1	7023	0.00033
cses:sector	49.6	1	7023	2.0e-12

In this case, with many schools and a moderate number of students within each school, the KR tests are essentially the same as Wald chisquare tests using the naively computed covariance matrix for the fixed effects:

> Anova(bryk.lmer.2)

Analysis of Deviance Table (Type II Wald chisquare tests)

Response: mathach

Chisq	\mathtt{Df}	Pr(>Chisq)
209.2	1	< 2e-16
409.4	1	< 2e-16
16.0	1	6.3e-05
12.9	1	0.00033
49.6	1	1.9e-12
	Chisq 209.2 409.4 16.0 12.9 49.6	Chisq Df 209.2 1 409.4 1 16.0 1 12.9 1 49.6 1

2.3 Examining the Random Effects: Computing BLUPs

The model bryk.lmer.2 includes a random intercept for each school. A natural question to ask in this problem is which schools have the largest intercepts, as these would be the highest achieving schools, and which schools have the smallest intercepts, as these are the schools that have the lowest math achievement. The model is given by Equation 4 (on page 15), with $b_{i2} = 0$, and so the intercept for the *i*th school is $\beta_1 + b_{i1}$ for public schools and $\beta_1 + b_{i1} + \beta_3$ for Catholic schools. In either case b_{i1} represents the difference between the mean for the *i*-th school and the mean for that school's sector.

Estimates for the intercept β_1 and for β_3 can be obtained from the summary output shown previously, and can be retrieved from the fitted model with

```
> fixef(bryk.lmer.2)
```

(Intercept)	meanses	cses	sectorCatholic
12.128	5.337	2.942	1.225
meanses:cses	cses:sectorCatholic		
1.044	-1.642		

The b_{i1} are random variables that are not directly estimated from the fitted model. Rather, **Ime4** computes the mode of the conditional distribution of each b_{i1} given the fitted model as predictions of the b_{i1} . Here are the first 6 of them:

8367 -3.6626

8854	-2.5948
4458	-0.5416
5762	-1.0094
6990	-2.7383
5815	-0.7584

Such "estimated" random effects (with "estimated" in quotes because the random-effect coefficients are random variables, not parameters) are often called *best linear unbiased predictors* or *BLUPs*.

The **ranef** function is very complicated because it needs to be able to accomodate complex models with one or more levels of hierarchy, and with one or more random effect per level in the hierarchy. The command **ranef(bryk.lmer.2)**\$school returns the random effects for schools as a matrix with one column.

To judge the size of the school random effects, the standard deviation of **mathach** for all students is about 7 units, and the average number of students per school is about 45, so the standard error of school average achievement is about $7/\sqrt{45} \approx 1$. A school intercept random effect of 2, for example, correponds to 2 standard deviations above average, and -2 is 2 standard deviations below average. Because the random effects are assumed to be normally distributed, we should expect to find few random effects predicted to be larger than about 3 or smaller than about -3.

The bottom and top 5 performing Catholic Schools can be identified as follows:

6808	-1.723
2658	-1.709
4292	1.701
2629	1.801
8193	2.810
8628	3.128
3427	4.215

The argument drop=FALSE is used in several places to force R to keep a one-column matrix as a matrix to preserve the row names, corresponding to school numbers. For public schools, we get

```
> pub.school.effects <- school.effects[!cat, 1, drop=FALSE]
> or <- order(pub.school.effects[, 1]) # order the school effects for Catholic Schools
> pub.school.effects[or, , drop=FALSE][c(1:5, 86:90), , drop=FALSE]
```

(Intercept) 8367 -3.663 4523 -3.546 3705 -3.180 7172 -2.766

8854	-2.595
6089	2.030
9198	2.077
6170	2.109
2655	3.053
7688	3.169

Possibly apart from school 6990, there were no extremely poorly performing Catholic schools, while there seem to be 2 or 3 highly performing schools. The public schools include a few very poorly performing schools and 2 highly performing schools.

2.4 An Illustrative Application to Longitudinal Data

To illustrate the use of linear mixed models in longitudinal research, we draw on data described by Davis et al. (2005) on the exercise histories of 138 teenaged girls hospitalized for eating disorders and of 93 comparable "control" subjects.¹⁰ The data are in the data frame Blackmore in the car package:

> head(Blackmore, 20)

	subject	age	exercise	group
1	100	8.00	2.71	patient
2	100	10.00	1.94	patient
3	100	12.00	2.36	patient
4	100	14.00	1.54	patient
5	100	15.92	8.63	patient
6	101	8.00	0.14	patient
7	101	10.00	0.14	patient
8	101	12.00	0.00	patient
9	101	14.00	0.00	patient
10	101	16.67	5.08	patient
11	102	8.00	0.92	patient
12	102	10.00	1.82	patient
13	102	12.00	4.75	patient
15	102	15.08	24.72	patient
16	103	8.00	1.04	patient
17	103	10.00	2.90	patient
18	103	12.00	2.65	patient
20	103	14.08	6.86	patient
21	104	8.00	2.75	patient
22	104	10.00	6.62	patient

The variables are:

• **subject**: an identification code; there are several observations for each subject, but because the girls were hospitalized at different ages, the number of observations and the age at the last observation vary.

¹⁰These data were generously made available to us by Elizabeth Blackmore and Caroline Davis of York University.

- age: the subject's age in years at the time of observation; all but the last observation for each subject were collected retrospectively at intervals of 2 years, starting at age 8.
- **exercise**: the amount of exercise in which the subject engaged, expressed as estimated hours per week.
- group: a factor indicating whether the subject is a "patient" or a "control".¹¹

2.4.1 Examining the Data

Initial examination of the data suggested that it is advantageous to take the log of exercise: Doing so makes the exercise distribution for both groups of subjects more symmetric and linearizes the relationship of exercise to age.¹² Because there are some 0 values of exercise, we use "started" logs in the analysis reported below (transformations are discussed in Fox and Weisberg, 2011, Section 3.4), adding 5 minutes (5/60 of an hour) to each value of exercise prior to taking logs (and using logs to the base 2 for interpretability):

```
> Blackmore$log.exercise <- log2(Blackmore$exercise + 5/60)
```

As in the analysis of the math-achievement data in the preceding section, we begin by sampling 20 subjects from each of the patient and control groups, plotting log.exercise against age for each subject:

```
> pat <- with(Blackmore, sample(unique(subject[group == "patient"]), 20))</pre>
> Pat.20 <- groupedData(log.exercise ~ age | subject,
                 data=Blackmore[is.element(Blackmore$subject, pat),])
+
> con <- with(Blackmore, sample(unique(subject[group == "control"]), 20))</pre>
> Con.20 <- groupedData(log.exercise ~ age | subject,</pre>
+
                 data=Blackmore[is.element(Blackmore$subject, con),])
 print(plot(Con.20, main="Control Subjects",
>
        xlab="Age", ylab="log2 Exercise",
+
+
        ylim=1.2*range(Con.20$log.exercise, Pat.20$log.exercise),
        layout=c(5, 4), aspect=1.0),
+
        position=c(0, 0, 0.5, 1), more=TRUE)
+
> print(plot(Pat.20, main="Patients",
        xlab="Age", ylab="log2 Exercise",
+
+
        ylim=1.2*range(Con.20$log.exercise, Pat.20$log.exercise),
+
        layout=c(5, 4), aspect=1.0),
        position=c(0.5, 0, 1, 1))
+
```

The graphs appear in Figure 7.

• Each Lattice plot is constructed by using the default plot method for grouped-data objects. Grouped-data objects, provided by the **nlme** package, are enhanced data frames, incorporating a model formula that gives information about the structure of the data. In this instance, the formula log.exercise ~ age | subject, read as "log.exercise depends on age given

¹¹To avoid the possibility of confusion, we point out that the variable group represents groups of independent patients and control subjects, and is *not* a factor defining clusters. Clusters in this longitudinal data set are defined by the variable subject.

¹²We invite the reader to examine the distribution of the **exercise** variable, before and after log-transformation.



Figure 7: \log_2 exercise by age for 20 randomly selected patients and 20 randomly selected control subjects.

subject," indicates that log.exercise is the response variable, age is the principal withinsubject covariate (actually, in this application, it is the *only* within-subject covariate), and the data are grouped by subject.

- To make the two plots comparable, we have exerted direct control over the scale of the vertical axis (set to slightly larger than the range of the combined log-exercise values), the layout of the plot (5 columns, 4 rows),¹³ and the aspect ratio of the plot (the ratio of the vertical to the horizontal size of the plotting region in each panel, set here to 1.0).
- The print method for Lattice objects, normally automatically invoked when the returned object is not assigned to a variable, simply plots the object on the active graphics device. So as to print both plots on the same "page," we have instead called print explicitly, using the position argument to place each graph on the page. The form of this argument is c(xmin, ymin, xmax, ymax), with horizontal (x) and vertical (y) coordinates running from 0, 0 (the lower-left corner of the page) to 1, 1 (the upper-right corner). The argument more=TRUE in the first call to print indicates that the graphics page is not yet complete.

There are few observations for each subject, and in many instances, no strong within-subject pattern. Nevertheless, it appears as if the general level of exercise is higher among the patients than among the controls. As well, the trend for exercise to increase with age appears stronger and more consistent for the patients than for the controls.

We pursue these impressions by fitting regressions of log.exercise on age for each subject. Because of the small number of observations per subject, we should not expect very good estimates of the within-subject regression coefficients. Indeed, one of the advantages of mixed models is that they can provide improved estimates of the within-subject coefficients (the random effects plus the fixed effects) by pooling information across subjects.¹⁴

```
> pat.list <- lmList(log.exercise ~ I(age - 8) | subject,
+ subset = group=="patient", data=Blackmore)
> con.list <- lmList(log.exercise ~ I(age - 8) | subject,
+ subset = group=="control", data=Blackmore)
> pat.coef <- coef(pat.list)
> con.coef <- coef(con.list)
> old <- par(mfrow=c(1, 2))
> boxplot(pat.coef[,1], con.coef[,1], main="Intercepts",
+ names=c("Patients", "Controls"))
> boxplot(pat.coef[,2], con.coef[,2], main="Slopes",
+ names=c("Patients", "Controls"))
> par(old)
```

Boxplots of the within-subjects regression coefficients are shown in Figure 8. We changed the origin of **age** to 8 years, which is the initial observation for each subject, so the intercept represents level of exercise at the start of the study. As expected, there is a great deal of variation in both the intercepts and the slopes. The median intercepts are similar for patients and controls, but there is somewhat more variation among patients. The slopes are higher on average for patients than for controls, for whom the median slope is close to 0.

¹³Notice the unusual ordering in specifying the layout — columns first, then rows.

¹⁴Pooled estimates of the random effects provide so-called *best-linear-unbiased predictors* (or *BLUPs*) of the regression coefficients for individual subjects. See help(predict.lme), Section 2.3, and the complementary readings.



Figure 8: Coefficients for the within-subject regressions of \log_2 exercise on age, for patients and control subjects.

2.4.2 Fitting a Mixed Model with Autocorrelated Errors

We proceed to fit a LMM to the data, including fixed effects for age (again, with an origin of 8), group, and their interaction, and random intercepts and slopes:

```
> bm.lme.1 <- lme(log.exercise ~ I(age - 8)*group,
                  random = ~ I(age - 8) | subject, data=Blackmore)
+
> summary(bm.lme.1)
Linear mixed-effects model fit by REML
 Data: Blackmore
  AIC BIC logLik
  3630 3669 -1807
Random effects:
Formula: ~I(age - 8) | subject
Structure: General positive-definite, Log-Cholesky parametrization
            StdDev Corr
(Intercept) 1.4436 (Intr)
I(age - 8) 0.1648 -0.281
Residual
            1.2441
Fixed effects: log.exercise ~ I(age - 8) * group
                          Value Std.Error DF t-value p-value
                                  0.18237 712 -1.514 0.1306
(Intercept)
                        -0.2760
                                                2.041 0.0416
I(age - 8)
                         0.0640
                                  0.03136 712
grouppatient
                        -0.3540
                                  0.23529 229
                                              -1.504 0.1338
I(age - 8):grouppatient 0.2399
                                  0.03941 712
                                               6.087 0.0000
Correlation:
                        (Intr) I(g-8) grpptn
I(age - 8)
                        -0.489
grouppatient
                        -0.775 0.379
I(age - 8):grouppatient 0.389 -0.796 -0.489
Standardized Within-Group Residuals:
             Q1
                    Med
   Min
                             QЗ
                                    Max
-2.7349 -0.4245 0.1228 0.5280
                                 2.6362
Number of Observations: 945
Number of Groups: 231
```

Examining the naive *t*-tests for the fixed effects, we start as usual with the test for the interactions, and in this case the interaction of **age** with **group** is highly significant, reflecting a much steeper average trend in the patient group. In light of the interaction, tests for the main effects of **age** and **group** are not of interest.¹⁵

¹⁵The **pbkrtest** package will not provide corrected standard errors and degrees of freedom for models fit by lme (as opposed to lmer).

We turn next to the random effects, and test whether the random intercepts and slopes are necessary, omitting each in turn from the model and calculating a likelihood-ratio statistic, contrasting the refitted model with the original model:

```
> bm.lme.2 <- update(bm.lme.1, random = ~ 1 | subject)</pre>
> anova(bm.lme.1, bm.lme.2) # test for random slopes
         Model df
                  AIC BIC logLik
                                      Test L.Ratio p-value
bm.lme.1
             1
                8
                  3630 3669
                             -1807
bm.lme.2
             2
                6
                  3644 3673
                             -1816 1 vs 2
                                             18.12 0.0001
> bm.lme.3 <- update(bm.lme.1, random = ~ I(age - 8) - 1 | subject)
> anova(bm.lme.1, bm.lme.3) # test for random intercepts
                  AIC BIC logLik
                                      Test L.Ratio p-value
         Model df
bm.lme.1
             1
                8 3630 3669
                             -1807
bm.lme.3
             2
                6 3834 3863
                             -1911 1 vs 2
                                             207.9 <.0001
```

The tests are highly statistically significant, suggesting that both random intercepts and random slopes are required.

Let us next consider the possibility that the within-subject errors (the ε_{ij} s in the mixed model of Equation 1 on page 2) are autocorrelated, as may well be the case, because the observations are taken longitudinally on the same subjects. The lme function incorporates a flexible mechanism for specifying error-correlation structures, and supplies constructor functions for several such structures.¹⁶ Most of these correlation structures, however, are appropriate only for equally spaced observations. An exception is the corCAR1 function, which permits us to fit a continuous first-order autoregressive process in the errors. Suppose that ε_{it} and $\varepsilon_{i,t+s}$ are errors for subject *i* separated by *s* units of time, where *s* need not be an integer; then, according to the continuous first-order autoregressive model, the correlation between these two errors is $\rho(s) = \phi^{|s|}$ where $0 \le \phi < 1$. This appears a reasonable specification in the current context, where there are at most $n_i = 5$ observations per subject.

Fitting the model with CAR1 errors to the data produces a convergence failure:

```
> bm.lme.4 <- update(bm.lme.1, correlation = corCAR1(form = ~ age | subject))
```

```
Error in lme.formula(fixed = log.exercise ~ I(age - 8) * group, data = Blackmore, :
nlminb problem, convergence error code = 1
message = iteration limit reached without convergence (10)
```

The correlation structure is given in the correlation argument to lme (here as a call to corCAR1); the form argument to corCAR1 is a one-sided formula defining the time dimension (here, age) and the group structure (subject). With so few observations within each subject, it is difficult to separate the estimated correlation of the errors from the correlations among the observations induced by clustering, as captured by subject-varying intercepts and slopes. This kind of convergence problem is a common occurrence in mixed-effects modeling.

We will therefore fit two additional models to the data, each including *either* random intercepts or random slopes (but not *both*) along with autocorrelated errors:

¹⁶A similar mechanism is provided for modeling non-constant error variance, via the weights argument to lme. See the documentation for lme for details. In contrast, the lmer function in the lme4 package does not accommodate autocorrelated errors, which is why we used lme for this example.

```
> bm.lme.5 <- update(bm.lme.1, random = ~ 1 | subject,
+ correlation = corCAR1(form = ~ age |subject)) # random intercepts (not slopes)
> bm.lme.6 <- update(bm.lme.1, random = ~ I(age - 8) - 1 | subject,
+ correlation = corCAR1(form = ~ age |subject)) # random slopes (not intercepts)
```

These models and our initial model without autocorrelated errors (bm.lme.1) are not properly nested for likelihood-ratio tests — indeed bm.lme.5 and bm.lme6 have the same number of parameters — but we can examine the maximized restricted log-likilihood under the models along with the AIC and BIC model-selection criteria:

All of these criteria point to model bm.lme.5, with random intercepts, a fixed age slope (within patient/control groups), and autocorrelated errors.

Although we expended some effort in modeling the random effects, the estimates of the fixed effects, and their standard errors, do not depend critically on the random-effect specification of the model, also a common occurrence:

```
> compareCoefs(bm.lme.1, bm.lme.5, bm.lme.6)
Call:
1: lme.formula(fixed = log.exercise ~ I(age - 8) * group, data = Blackmore,
  random = ~I(age - 8) | subject)
2: lme.formula(fixed = log.exercise ~ I(age - 8) * group, data = Blackmore,
 random = ~1 | subject, correlation = corCAR1(form = ~age | subject))
3: lme.formula(fixed = log.exercise ~ I(age - 8) * group, data = Blackmore,
  random = ~I(age - 8) - 1 | subject, correlation = corCAR1(form = ~age |
  subject))
                                   SE 1 Est. 2
                        Est. 1
                                                   SE 2 Est. 3
                                                                   SE 3
(Intercept)
                        -0.2760
                                0.1824 -0.3070 0.1895 -0.3178
                                                                 0.1935
I(age - 8)
                        0.0640
                                 0.0314 0.0728 0.0317 0.0742
                                                                 0.0365
grouppatient
                        -0.3540
                                 0.2353 -0.2838
                                                0.2447 -0.2487
                                                                 0.2500
I(age - 8):grouppatient 0.2399
                                0.0394 0.2274 0.0397 0.2264 0.0460
```

The summary for model bm.lme.5 is as follows:

```
> summary(bm.lme.5)
```

bm.lme.6 -1803 3654 3620

```
Linear mixed-effects model fit by REML
 Data: Blackmore
   AIC BIC logLik
  3605 3639 -1795
Random effects:
Formula: ~1 | subject
        (Intercept) Residual
               1.15
StdDev:
                      1.529
Correlation Structure: Continuous AR(1)
 Formula: ~age | subject
Parameter estimate(s):
   Phi
0.6312
Fixed effects: log.exercise ~ I(age - 8) * group
                          Value Std.Error DF t-value p-value
(Intercept)
                       -0.30697
                                  0.18950 712 -1.620 0.1057
I(age - 8)
                         0.07278 0.03168 712
                                                2.297 0.0219
grouppatient
                       -0.28383 0.24467 229 -1.160 0.2472
I(age - 8):grouppatient 0.22744 0.03974 712 5.723 0.0000
Correlation:
                        (Intr) I(g-8) grpptn
I(age - 8)
                        -0.553
grouppatient
                       -0.775 0.428
I(age - 8):grouppatient 0.441 -0.797 -0.556
Standardized Within-Group Residuals:
                    Med
    Min
             Q1
                             Q3
                                    Max
-2.9431 -0.4640 0.1732 0.5869
                                2.0220
Number of Observations: 945
Number of Groups: 231
```

There is, therefore, a moderately large estimated error autocorrelation, $\hat{\phi} = .631$.

To get a more concrete sense of the fixed effects, using model bm.lme.5 (which includes autocorrelated errors and random intercepts, but not random slopes), we employ the predict method for lme objects to calculate fitted values for patients and controls across the range of ages (8 to 18) represented in the data:

1.4430

3

12 patient

0.610082



Figure 9: Fitted values representing estimated fixed effects of group, age, and their interaction.

4	14	patient	1.210523	2.2309
5	16	patient	1.810964	3.4254
6	18	patient	2.411405	5.2366
7	8	control	-0.306970	0.7250
8	10	control	-0.161409	0.8108
9	12	control	-0.015847	0.9057
10	14	control	0.129715	1.0107
11	16	control	0.275277	1.1269
12	18	control	0.420838	1.2554

Specifying level=0 in the call to predict produces estimates of the fixed effects. The expression 2^pdata\$log.exercise - 5/60 translates the fitted values of exercise from the log₂ scale back to hours/week.

Finally, we plot the fitted values (Figure 9):

```
> plot(pdata$age, pdata$exercise, type="n",
+ xlab="Age (years)", ylab="Exercise (hours/week)")
> points(pdata$age[1:6], pdata$exercise[1:6], type="b", pch=19, lwd=2)
> points(pdata$age[7:12], pdata$exercise[7:12], type="b", pch=22, lty=2, lwd=2)
> legend("topleft", c("Patients", "Controls"), pch=c(19, 22),
+ lty=c(1,2), lwd=2, inset=0.05)
```

Essentially the same graph (Figure 10) can be constructed by the **effects** package, with the added feature of confidence intervals for the estimated effects:

```
> plot(Effect(c("age", "group"), bm.lme.5, xlevels=list(age=seq(8, 18, by=2)),
+ transformation=list(link=function(x) log2(x + 5/60),
+ inverse=function(x) 2<sup>x</sup> - 5/60)),
```



Figure 10: Plot produced using the Effect function in the effects package.

```
+ multiline=TRUE, ci.style="bars",
+ xlab="Age (years)", ylab="Exercise (hours/week)",
+ rescale.axis=FALSE, rug=FALSE, colors=c("black", "black"),
+ key.args=list(x = 0.20, y = 0.75, corner = c(0, 0), padding.text = 1.25),
+ main="")
```

It is apparent that the two groups of subjects have similar average levels of exercise at **age 8**, but that thereafter the level of exercise increases much more rapidly for the patient group than for the controls.

3 Generalized Linear Mixed Models

Generalized linear mixed models (GLMMs) bear the same relationship to LMMs that GLMs bear to linear models (see Fox and Weisberg, 2011, Chapters 4–5). GLMMs add random effects to the linear predictor of a GLM and express the expected value of the response conditional on the random effects: The link function $g(\cdot)$ is the same as in generalized linear models. For a GLMM with two levels of hierarchy, the conditional distribution of y_{ij} , the response for observation j in group i, given the random effects, is (most straightforwardly) a member of an exponential family, with mean μ_{ij} , variance

$$\operatorname{Var}(y_{ij}) = \phi V(\mu_{ij})\lambda_{ij}$$

and covariances

$$\operatorname{Cov}(y_{ij}, y_{ij'}) = \phi \sqrt{V(\mu_{ij})} \sqrt{V(\mu_{ij'})} \lambda_{ijj'}$$

where ϕ is a dispersion parameter and the function $V(\mu_{ij})$ depends on the distributional family to which Y belongs. For example, in the binomial and Poisson families the dispersion is fixed to 1, and in the Gaussian family $V(\mu) = 1$. Alternatively, for quasi-likelihood estimation, $V(\cdot)$ can be given directly.¹⁷

The GLMM may therefore be written as

$$\begin{aligned} \eta_{ij} &= \beta_1 + \beta_2 x_{2ij} + \dots + \beta_p x_{pij} + b_{1i} z_{1ij} + \dots + b_{qi} z_{qij} \\ g(\mu_{ij}) &= E(y_{ij} | b_{1i}, \dots, b_{qi}) = \eta_{ij} \\ b_{ki} &\sim N(0, \psi_k^2), \operatorname{Cov}(b_{ki}, b_{k'i}) = \psi_{kk'} \\ b_{ki}, b_{k'i'} \text{ are independent for } i \neq i' \\ \operatorname{Var}(y_{ij}) &= \phi V(\mu_{ij}) \lambda_{ij} \\ \operatorname{Cov}(y_{ij}, y_{ij'}) &= \phi \sqrt{V(\mu_{ij})} \sqrt{V(\mu_{ij'})} \lambda_{ijj'} \\ y_{ij}, y_{ij'} \text{ are independent for } i \neq i' \end{aligned}$$

where η_{ij} is the linear predictor for observation j in cluster i; the fixed-effect coefficients (β s), random-effect coefficients (bs), fixed-effect regressors (xs), and random-effect regressors (zs) are defined as in the LMM.¹⁸

In matrix form, the GLMM is

$$\eta_{i} = \mathbf{X}_{i}\boldsymbol{\beta} + \mathbf{Z}_{i}\mathbf{b}_{i}$$

$$g(\boldsymbol{\mu}_{i}) = g[E(\mathbf{y}_{i}|\mathbf{b}_{i})] = \boldsymbol{\eta}_{i}$$

$$\mathbf{b}_{i} \sim \mathbf{N}_{q}(\mathbf{0}, \boldsymbol{\Psi})$$

$$(6)$$

 $\mathbf{b}_i, \mathbf{b}_{i'}$ are independent for $i \neq i'$

$$E(\mathbf{y}_i|\mathbf{b}_i) = \boldsymbol{\mu}_i \tag{7}$$

$$V(\mathbf{y}_i|\mathbf{b}_i) = \phi V^{1/2}(\boldsymbol{\mu}_i) \boldsymbol{\Lambda}_i V^{1/2}(\boldsymbol{\mu}_i)$$
(8)

 $\mathbf{y}_i, \mathbf{y}_{i'}$ are independent for $i \neq i'$

where

- \mathbf{y}_i is the $n_i \times 1$ response vector for observations in the *i*th of *m* groups;
- μ_i is the $n_i \times 1$ expectation vector for the response, conditional on the random effects;
- η_i is the $n_i \times 1$ linear predictor for the elements of the response vector;
- $g(\cdot)$ is the link function, transforming the conditional expected response to the linear predictor;
- \mathbf{X}_i is the $n_i \times p$ model matrix for the fixed effects of observations in group *i*;
- β is the $p \times 1$ vector of fixed-effect coefficients;
- \mathbf{Z}_i is the $n_i \times q$ model matrix for the random effects of observations in group *i*;
- \mathbf{b}_i is the $q \times 1$ vector of random-effect coefficients for group i;
- Ψ is the $q \times q$ covariance matrix of the random effects;
- Λ_i is $n_i \times n_i$ and expresses the dependence structure for the conditional distribution of the response within each group—for example, if the observations are sampled independently in each group, $\Lambda_i = \mathbf{I}_{n_i}$;¹⁹

¹⁷As in the generalized linear model (Fox and Weisberg, 2011, Section 10.5.3).

¹⁸ The glmer function in the lme4 package that we will use to fit GLMMs is somewhat more restrictive, setting $\lambda_{kk} = 1$ and $\lambda_{kk'} = 0$.

¹⁹As mentioned, this restriction is imposed by the glmer function in the lme4 package. See footnote 18.

- $V^{1/2}(\boldsymbol{\mu}_i) \equiv \text{diag}[\sqrt{V(\boldsymbol{\mu}_{ij})}];$ and
- ϕ is the dispersion parameter.

3.1 Example: Migraine Headaches

In an effort to reduce the severity and frequency of migraine headaches through the use of biofeedback training, Tammy Kostecki-Dillon collected longitudinal data on migraine-headache sufferers.²⁰ The 133 patients who participated in the study were each given four weekly sessions of biofeedback training. The patients were asked to keep daily logs of their headaches for a period of 30 days prior to training, during training, and post-training, to 100 days after training began. Compliance with these instructions was low, and there is therefore quite a bit of missing data; for example, only 55 patients kept a log prior to training. On average, subjects recorded information on 31 days, with the number of days ranging from 7 to 121. Subjects were divided into three self-selected groups: those who discontinued their migraine medication during the training and post-training phase of the study; those who continued their medication, but at a reduced dose; and those who continued their medication at the previous dose.

We will use a binomial GLMM—specifically, a binary logit mixed-effects model—to analyze the incidence of headaches during the period of the study. Examination of the data suggested that the incidence of headaches was constant during the pre-training phase of the study, increased, as was expected by the investigator, at the start of training, and then declined at a decreasing rate. We decided to fit a linear trend prior to the start of training (before time 0), possibly to capture a trend that we failed to detect in our exploration of the data; and to transform time at day 1 and later (which, for simplicity, we term "time post-treatment") by taking the square-root.²¹ In addition to the intercept, representing the level of headache incidence at the end of the pre-training period, we include a dummy regressor coded 1 post-treatment, and 0 pre-treatment, to capture the anticipated increase in headache incidence at the start of training; dummy regressors for levels of medication; and interactions between medication and treatment, and between medication and the pre- and post-treatment time trends. Thus, the fixed-effects part of the model is

$$logit(\mu_{ij}) = \beta_1 + \beta_2 m_{1i} + \beta_3 m_{2i} + \beta_4 p_{ij} + \beta_5 t_{0ij} + \beta_6 \sqrt{t_{1ij}} + \beta_7 m_{1i} p_{ij} + \beta_8 m_{2i} p_{ij} + \beta_9 m_{1i} t_{0ij} + \beta_{10} m_{2i} t_{0ij} + \beta_{11} m_{1i} \sqrt{t_{1ij}} + \beta_{12} m_{2i} \sqrt{t_{1ij}}$$

where

- μ_{ij} is the probability of a headache for individual i = 1, ..., 133, on occasion $j = 1, ..., n_i$, conditional on the random effects;
- m_{1i} and m_{2i} are the dummy regressors for a factor medication with levels none, reduced and continuing for no medication, reduced medication, and no change in medication;
- p_{ij} is a dummy regressor for a factor treatment with levels no and yes;
- t_{0ij} is time (in days) pre-treatment in a variable pretime, running from -29 through 0, and coded 0 after treatment began; and

²⁰The data are described by Kostecki-Dillon, Monette, and Wong (1999) and were generously made available by Georges Monette, who performed the original data analysis. The analysis reported here is similar to his.

²¹The original analysis of the data by Georges Monette used regression splines for time-trends, with results generally similar to those reported here.

• t_{1ij} is time (in days) post-treatment in a variable posttime, running from 1 through 99, and coded 0 pre-treatment.

This specification for the fixed-effects can be summarized in the matrix **X** with 12 columns correponding to the regressors multipying each of the 12 β s in the fixed-effects part of the model.

For random effects, we allow a separate random intercept for pre- and post-treatment by including both the intercept and treatment among the random effects. In addition, we allow random slopes for both pretreat and posttreat. The matrix \mathbf{Z} will have 4 columns, and the corresponding coviarance matrix $\boldsymbol{\Psi}$ has 4 variance terms and 6 covariance terms for a total of 10 parameters, complexity that can cause numerical problems as we will see shortly.

The data for this example are in the KosteckiDillon data frame in the car package. We begin with a bit of data-management to compute the variables needed from those already in the data set:

```
> KosteckiDillon$treatment <- factor(with(KosteckiDillon,
+ ifelse(time > 0, "yes", "no")))
> KosteckiDillon$pretreat <- with(KosteckiDillon, ifelse(time > 0, 0, time))
> KosteckiDillon$posttreat <- with(KosteckiDillon, ifelse(time > 0, time, 0))
> head(KosteckiDillon, 10)
```

	id	time	dos	hatype	age	airq	medication	headache	sex	${\tt treatment}$	pretreat
1	1	-11	753	Aura	30	9	continuing	yes	female	no	-11
2	1	-10	754	Aura	30	7	continuing	yes	female	no	-10
3	1	-9	755	Aura	30	10	continuing	yes	female	no	-9
4	1	-8	756	Aura	30	13	continuing	yes	female	no	-8
5	1	-7	757	Aura	30	18	continuing	yes	female	no	-7
6	1	-6	758	Aura	30	19	continuing	yes	female	no	-6
7	1	-5	759	Aura	30	17	continuing	yes	female	no	-5
8	1	22	786	Aura	30	21	continuing	yes	female	yes	0
9	1	23	787	Aura	30	21	continuing	yes	female	yes	0
10	1	24	788	Aura	30	18	continuing	yes	female	yes	0
posttreat											
1			0								
2			0								
3			0								
4			0								
5			0								
6			0								
7			0								
8			22								
9			23								
10		2	24								

There are variables in the data set that we will not use in the example in this section; for details, see ?KosteckiDillon.

GLMMs may be fit by the glmer function (pronounced "glimmer") in the lme4 package. As is also true for lmer, there is no provision for autocorrelated within-subject errors, and in the case of a GLMM, we don't have the alternative of using the nlme package. Even without explicit termporal autocorrelation, however, the random effects are complex for a fairly small data set, and we will try to simplify this part of the model. Specifying fixed and random effects in glmer is the same as in lmer; additionally, as for glm, we may specify a distributional family argument, which, in turn, takes an optional link argument. In the current example, we use the default logit link for the binomial family, and so do not have to give the link explicitly.

Our initial attempt to fit a GLMM to the migraine-headaches data produces a convergence warning:

```
> mod.mig.1 <- glmer(headache ~ # warning: time-consuming!
+ medication * (treatment + pretreat + sqrt(posttreat))
+ (treatment + pretreat + sqrt(posttreat) | id),
+ data=KosteckiDillon, family=binomial)
```

Warning message:

```
In checkConv(attr(opt, "derivs"), opt$par, ctrl = control$checkConv, :
   Model failed to converge with
   max|grad| = 0.00623063 (tol = 0.001, component 2)
```

Failure to converge is a common occurence in fitting a GLMM, and the computations are complex. In this example, the function to be maximized to find the estimates is 22-dimensional, with 12 fixed-effects parameters and 10 more parameters in Ψ . There are multiple possible causes for the failure to converge; sometimes changing to a different optimizer in the computations can produce convergence. The glmer function makes provision for alternative optimizers, and after a bit of experimentation, we were able to obtain convergence using the optimx optimizer in the **optimx** package, specifying the optimization method as "nlminb"; optimx produces its own warning but nevertheless converges to a solution:

```
> library(optimx)
> mod.mig.1a <- glmer(headache ~</pre>
          medication * (treatment + pretreat + sqrt(posttreat))
+
+
          + (treatment + pretreat + sqrt(posttreat) | id),
      data=KosteckiDillon, family=binomial,
+
+
      control=glmerControl(optimizer="optimx",
                            optCtrl=list(method="nlminb")))
+
Warning message:
In optimx.check(par, optcfg$ufn, optcfg$ugr, optcfg$uhess, lower, :
 Parameters or bounds appear to have different scalings.
  This can cause poor performance in optimization.
  It is important for derivative free methods like BOBYQA, UOBYQA, NEWUOA.
As it turns out, the two solutions are nearly identical:
> compareCoefs(mod.mig.1, mod.mig.1a)
Call:
1: glmer(formula = headache ~ medication * (treatment + pretreat +
  sqrt(posttreat)) + (treatment + pretreat + sqrt(posttreat) | id), data =
  KosteckiDillon, family = binomial)
2: glmer(formula = headache ~ medication * (treatment + pretreat +
  sqrt(posttreat)) + (treatment + pretreat + sqrt(posttreat) | id), data = KD,
  family = binomial, control = glmerControl(optimizer = "optimx", optCtrl =
```

list(method = "nlminb")))

	Est. 1	SE 1	Est. 2	SE 2
(Intercept)	2.27e-01	6.12e-01	2.27e-01	6.12e-01
medicationreduced	1.96e+00	8.86e-01	1.96e+00	8.86e-01
medicationcontinuing	2.79e-01	6.86e-01	2.79e-01	6.86e-01
treatmentyes	3.38e-01	7.12e-01	3.40e-01	7.12e-01
pretreat	-1.95e-02	4.18e-02	-1.97e-02	4.19e-02
sqrt(posttreat)	-2.72e-01	9.21e-02	-2.72e-01	9.22e-02
medicationreduced:treatmentyes	4.51e-01	1.03e+00	4.47e-01	1.04e+00
medicationcontinuing:treatmentyes	1.16e+00	8.13e-01	1.16e+00	8.14e-01
medicationreduced:pretreat	6.22e-02	6.03e-02	6.26e-02	6.03e-02
medicationcontinuing:pretreat	-6.59e-06	4.76e-02	2.40e-04	4.77e-02
<pre>medicationreduced:sqrt(posttreat)</pre>	-1.05e-02	1.29e-01	-1.04e-02	1.29e-01
<pre>medicationcontinuing:sqrt(posttreat)</pre>	1.56e-02	1.13e-01	1.55e-02	1.13e-01

The convergence warning in our initial attempt was likely a false alarm; in general, glmer is conservative about detecting convergence failures. Existing methods are approximations because exact evaluation of the likelihood is intractable. The glmer function implements various numerical methods, and by default uses a Laplace approximation, which is a compromise between accuracy and computational speed.

Type-II Wald tests for the fixed effects, computed by the Anova function in the **car** package, reveal that all of the interactions are non-significant, along with the pre-treatment trend, while the medication and treatment effects, along with the post-treatment trend, are highly statistically significant:

> Anova(mod.mig.1a)

Analysis of Deviance Table (Type II Wald chisquare tests)

Response: headache

-	Chisq	\mathtt{Df}	Pr(>Chisq)
medication	22.34	2	1.4e-05
treatment	13.32	1	0.00026
pretreat	0.38	1	0.53782
sqrt(posttreat)	34.60	1	4.1e-09
medication:treatment	2.38	2	0.30357
medication:pretreat	1.86	2	0.39392
<pre>medication:sqrt(posttreat)</pre>	0.06	2	0.96955

Before examining the estimated fixed effects in the model, we will attempt to simplify the random effects, removing each random effect in turn and performing a likelihood-ratio test relative to the initial model.

```
> mod.mig.2 <- update(mod.mig.1a,
+ formula = headache ~
+ medication * (treatment + pretreat + sqrt(posttreat))
+ + (-1 + as.numeric(treatment == "yes") + pretreat + sqrt(posttreat) | id))
> anova(mod.mig.1a, mod.mig.2)
```

```
Data: KosteckiDillon
Models:
mod.mig.2: headache ~ medication + treatment + pretreat + sqrt(posttreat) +
               (-1 + as.numeric(treatment == "yes") + pretreat + sqrt(posttreat) |
mod.mig.2:
mod.mig.2:
                   id) + medication:treatment + medication:pretreat + medication:sqrt(posttreat
mod.mig.1a: headache ~ medication * (treatment + pretreat + sqrt(posttreat)) +
                (treatment + pretreat + sqrt(posttreat) | id)
mod.mig.1a:
           Df AIC BIC logLik deviance Chisq Chi Df Pr(>Chisq)
mod.mig.2 18 4384 4498 -2174
                                   4348
mod.mig.1a 22 4373 4512 -2164
                                   4329
                                         19.7
                                                   4
                                                        0.00057
> pvalCorrected(19.701, df=4) # no random intercepts
[1] 0.0003839
> mod.mig.3 <- update(mod.mig.1a,</pre>
+
      formula = headache ~
          medication * (treatment + pretreat + sqrt(posttreat))
+
      + (pretreat + sqrt(posttreat) | id))
+
> anova(mod.mig.1a, mod.mig.3)
Data: KosteckiDillon
Models:
mod.mig.3: headache ~ medication + treatment + pretreat + sqrt(posttreat) +
               (pretreat + sqrt(posttreat) | id) + medication:treatment +
mod.mig.3:
mod.mig.3:
               medication:pretreat + medication:sqrt(posttreat)
mod.mig.1a: headache ~ medication * (treatment + pretreat + sqrt(posttreat)) +
                (treatment + pretreat + sqrt(posttreat) | id)
mod.mig.1a:
               AIC BIC logLik deviance Chisq Chi Df Pr(>Chisq)
           Df
mod.mig.3 18 4377 4491 -2170
                                   4341
mod.mig.1a 22 4373 4512 -2164
                                   4329 12.1
                                                   4
                                                          0.017
> pvalCorrected(12.092, df=4) # no random treatment
[1] 0.01188
> mod.mig.4 <- update(mod.mig.1a,</pre>
      formula = headache ~
          medication * (treatment + pretreat + sqrt(posttreat))
+
      + (treatment + sqrt(posttreat) | id))
+
> anova(mod.mig.1a, mod.mig.4)
Data: KosteckiDillon
Models:
mod.mig.4: headache ~ medication + treatment + pretreat + sqrt(posttreat) +
               (treatment + sqrt(posttreat) | id) + medication:treatment +
mod.mig.4:
               medication:pretreat + medication:sqrt(posttreat)
mod.mig.4:
mod.mig.1a: headache ~ medication * (treatment + pretreat + sqrt(posttreat)) +
                (treatment + pretreat + sqrt(posttreat) | id)
mod.mig.1a:
```

```
AIC BIC logLik deviance Chisq Chi Df Pr(>Chisq)
           Df
mod.mig.4 18 4370 4484
                         -2167
                                    4334
mod.mig.1a 22 4373 4512 -2164
                                    4329
                                           5.8
                                                    4
                                                            0.21
> pvalCorrected(5.7963, df=4) # no random pretreat
[1] 0.1684
> mod.mig.5 <- update(mod.mig.1, # this fails with mod.mig.1a</pre>
      formula = headache ~
+
+
          medication * (treatment + pretreat + sqrt(posttreat))
      + (treatment + pretreat | id))
+
> anova(mod.mig.1, mod.mig.5)
Data: KosteckiDillon
Models:
mod.mig.5: headache ~ medication + treatment + pretreat + sqrt(posttreat) +
               (treatment + pretreat | id) + medication:treatment + medication:pretreat +
mod.mig.5:
mod.mig.5:
               medication:sqrt(posttreat)
mod.mig.1: headache ~ medication * (treatment + pretreat + sqrt(posttreat)) +
mod.mig.1:
               (treatment + pretreat + sqrt(posttreat) | id)
              AIC BIC logLik deviance Chisq Chi Df Pr(>Chisq)
          Df
mod.mig.5 18 4381 4495
                        -2172
                                  4345
mod.mig.1 22 4373 4512
                                   4329
                                        16.2
                                                   4
                                                         0.0027
                        -2164
> pvalCorrected(16.214, df=4) # no random posttreat
```

[1] 0.001885

As in LMMs, we use our pvalCorrected function to correct chisquare tests for the variance/ covariance components, reflecting the fact that the null values of variances are on the boundary of the parameter space. As well, we were unable to fit mod.mig.5 using optimx without producing an error, and so we updated mod.mig.1 rather than mod.mig.1a to obtain mod.mig.5 and the corresponding test for the random post-treatment effect.

The relatively convoluted specification of mod.mig.2, where the dummy regressor for treatment is generated directly, rather than putting the factor treatment in the random-effects formula, is necessary to suppress the random effect for the intercept; simply specifying -1 with the factor treatment in the random-effects formula places *two* dummy regressors in the random-effects model, fitting different intercepts for each of the two levels of treatment, and producing a model equivalent to mod.mig.1a. This is a general property of R model formulas that we view as generally desirable, making it difficult to fit models that violate the principal of marginality. In the current application, however, the intercept represents the level of the headache logit immediately prior to the onset of treatment, while the coefficient of the treatment dummy regressor represents the change in level at the onset of treatment. It is perfectly possible that random effects are required for one of these coefficients but not the other. Although the test for random intercepts in the presence of the treatment factor makes for a more complicated example, we think that it is worthwhile explaining how a test like this can be conducted.

On the basis of these tests for the fixed and random effects, we specified a final model for the migraines data that eliminates the fixed-effect interactions with medication and the pre-treatment trend fixed and random effects, obtaining the following estimates for the fixed effects and variance components:

```
> mod.mig.6 <- glmer(headache ~ medication + treatment + sqrt(posttreat)</pre>
      + (treatment + sqrt(posttreat) | id),
+
      data=KosteckiDillon, family=binomial,
+
      control=glmerControl(optimizer="optimx",
+
          optCtrl=list(method="nlminb")))
+
> summary(mod.mig.6)
Generalized linear mixed model fit by maximum likelihood (Laplace
  Approximation) [glmerMod]
 Family: binomial (logit)
Formula: headache ~ medication + treatment + sqrt(posttreat) + (treatment +
    sqrt(posttreat) | id)
  Data: KosteckiDillon
Control: glmerControl(optimizer = "optimx", optCtrl = list(method = "nlminb"))
     AIC
                    logLik deviance df.resid
              BIC
    4369
             4439
                     -2174
                               4347
                                        4141
Scaled residuals:
  Min
           1Q Median
                         ЗQ
                               Max
-5.182 -0.646 0.260 0.580 3.690
Random effects:
                        Variance Std.Dev. Corr
 Groups Name
 id
        (Intercept)
                        1.7011
                                 1.304
        treatmentyes
                        1.7126
                                 1.309
                                          -0.12
                                           0.11 -0.66
        sqrt(posttreat) 0.0571
                                 0.239
Number of obs: 4152, groups: id, 133
Fixed effects:
                     Estimate Std. Error z value Pr(>|z|)
(Intercept)
                                  0.3438
                                           -0.72
                      -0.2459
                                                    0.4745
medicationreduced
                       2.0501
                                  0.4679
                                            4.38 1.2e-05
medicationcontinuing
                                            3.01
                       1.1553
                                  0.3838
                                                    0.0026
treatmentyes
                       1.0608
                                  0.2439
                                            4.35 1.4e-05
sqrt(posttreat)
                                           -5.98 2.2e-09
                      -0.2684
                                  0.0449
Correlation of Fixed Effects:
            (Intr) mdctnr mdctnc trtmnt
medictnrdcd -0.674
mdctncntnng -0.828 0.656
treatmentys -0.215 -0.053 -0.049
sqrt(psttr) 0.016 -0.009 -0.002 -0.685
```

Figure 11 shows the estimated fixed effects plotted on the probability scale; as a consequence, the post-treatment trends for the three medication conditions are not parallel, as they would be if plotted on the logit scale:

> new.1 <- expand.grid(treatment="yes", posttreat=1:99,</pre>

```
medication=c("reduced", "continuing", "none"))
+
> new.1$treatment <- factor("yes", levels=c("no", "yes"))</pre>
> new.2 <- expand.grid(treatment="no", posttreat=-29:0,</pre>
      medication=c("reduced", "continuing", "none"))
+
> new.2$posttreat <- 0
> new.2$treatment <- factor("no", levels=c("no", "yes"))</pre>
> new <- rbind(new.2, new.1)</pre>
> new$p <- predict(mod.mig.6, newdata=new, re.form=NA, type="response")</pre>
> new$time <- c(rep(-29:0, 3),rep(1:99, 3))
> plot(p ~ time, type="n", data=new, xlab="Time (days)",
      vlab="Fitted Probability of Headache")
> abline(v=0, col="gray")
> lines(p ~ time, subset = medication == "none", data=new,
      ltv=1, lwd=2)
+
> lines(p ~ time, subset = medication == "reduced", data=new,
      lty=2, lwd=2)
+
> lines(p ~ time, subset = medication == "continuing", data=new,
      lty=3, lwd=2)
+
> legend("topright", lty=1:3, lwd=2,
      legend=c("none", "reduced", "continuing"), title="Medication",
+
+
      inset=.02)
```

It is apparent from this graph that after an initial increase at the start of treatment, the incidence of headaches declined to substantially below its pre-treatment level. As well, the incidence of headaches was lowest among the patients who discontinued their medication, and highest among those who reduced their medication; patients who continued their medication at pre-training levels were intermediate in headache incidence. Of course, self-selection of the medication groups renders interpretation of this pattern ambiguous.

4 Nonlinear Mixed Models

One extension of the nonlinear regression model (see our appendix on nonlinear regression) to include random effects, due to Pinheiro and Bates (2000) and fit by the nlme function in the nlme package,²² is as follows (but with different notation than in the original source):

$$\mathbf{y}_{i} = f(\boldsymbol{\theta}_{i}, \mathbf{X}_{i}) + \boldsymbol{\varepsilon}_{i}$$

$$\boldsymbol{\theta}_{i} = \mathbf{A}_{i}\boldsymbol{\beta} + \mathbf{B}_{i}\boldsymbol{\delta}_{i}$$
(9)

where

- \mathbf{y}_i is the $n_i \times 1$ response vector for the n_i observations in the *i*th of *m* groups.
- \mathbf{X}_i is a $n_i \times s$ matrix of explanatory variables (some of which may be categorical) for observations in group *i*.
- $\varepsilon_i \sim \mathbf{N}_{n_i}(\mathbf{0}, \sigma_{\varepsilon}^2 \mathbf{\Lambda}_i)$ is a $n_i \times 1$ vector of multivariately normally distributed errors for observations in group *i*; the matrix $\mathbf{\Lambda}_i$, which is $n_i \times n_i$, is typically parametrized in terms of a much

 $^{^{22}}$ The **lme4** package also has some facilities for fitting nonlinear mixed models, but these are preliminary at the time that we are writing this appendix.



Figure 11: Fixed effects from a binomial GLMM fit to the migraines data. Treatment started at time 1.

smaller number of parameters, and $\Lambda_i = \mathbf{I}_{n_i}$ if the observations are independently sampled within groups.

- θ_i is a $n_i \times 1$ composite coefficient vector for the observations in group *i*, incorporating both fixed and random effects.
- β is the $p \times 1$ vector of fixed-effect parameters.
- $\delta_i \sim \mathbf{N}_q(\mathbf{0}, \Psi)$ is the $q \times 1$ vector of random-effect coefficients for group *i*.
- \mathbf{A}_i and \mathbf{B}_i are, respectively, $n_i \times p$ and $n_i \times q$ matrices of known constants for combining the fixed and random effects in group *i*. These will often be "incidence matrices" of 0s and 1s but may also include level-1 explanatory variables, treated as conditionally fixed (as in the standard linear model).

Like fundamentally nonlinear fixed-effects regression models, nonlinear mixed-effects models (NLMMs) are uncommon in the social and behavioral sciences. As the following example illustrates, however, it is occasionally natural to specify a nonlinear mixed model, especially when the parameters of the model have compelling substantive interpretations.

4.1 Example: Recovery From Coma

The data and model for this example are taken from Wong et al. (2001).²³ The data pertain to 200 patients who sustained traumatic brain injuries resulting in comas of varying duration. After awakening from their comas, patients were periodically administered a standard IQ test. In this section, we will examine recovery of "performance IQ" ("PIQ") post-coma; the data set, in the Wong

 $^{^{23}}$ We are grateful to Georges Monette for making the data and associated materials available. The analysis reported here is very similar to that in the original source.

data frame provided by the **car** package, also includes a measure of verbal IQ. Here are the first few observations in the data set:

> head(Wong)

	id	days	duration	sex	age	piq	viq
1	3358	30	4	Male	20.67	87	89
2	3535	16	17	Male	55.29	95	77
3	3547	40	1	Male	55.92	95	116
4	3592	13	10	Male	61.66	59	73
5	3728	19	6	Male	30.13	67	73
6	3790	13	3	Male	57.06	76	69

About half of the patients in the study (107) completed a single IQ test, but the remainder were measured on two to five irregularly timed occasions, raising the possibility of tracing the trajectory of IQ recovery post-coma. A mixed-effects model is very useful here because it allows us to pool the information in the small number of observations available per patient (on average 331/200 = 1.7) to estimate the typical within-subject trajectory of recovery along with variation in this trajectory.

After examining the data, Wong et al. posited the following *asymptotic growth model* for IQ recovery:

$$Y_{ij} = \theta_{1i} + \theta_{2i}e^{-\theta_{3i}X_{1ij}} + \varepsilon_{ij}$$

$$\theta_{1i} = \beta_1 + \beta_2\sqrt{X_{2i}} + \delta_{1i}$$

$$\theta_{2i} = \beta_3 + \beta_4\sqrt{X_{2i}} + \delta_{2i}$$

$$\theta_{3i} = \beta_5$$

$$(10)$$

where the variables and parameters of the model have the following interpretations (see Figure 12):

- Y_{ij} is the PIQ of the *i*th patient (with patients indexed by id in the Wong data set) measured on the *j*th occasion, $j = 1, ..., n_i$; as mentioned, $n_i = 1$ for about half the patients.
- X_{1ij} is the time post-coma (in days) for the *i*th patient at the *j*th occasion (the variable days in the data set).
- X_{2i} is the duration of the coma (in days) for the *i*th patient (duration in the data set).
- θ_{1i} is the eventual, recovered level of PIQ for patient *i*, specified to depend linearly on the square-root of the length of the coma, with fixed-effect parameters β_1 and β_2 , and a random-effect component δ_{1i} . Were patients to recover PIQ fully, the average value of θ_{1i} would be 100, assuming that coma patients are representative of the general population in their precoma average level of IQ. Thus, the fixed-effect intercept β_1 is interpretable as the expected eventual level of PIQ for a patient in a coma of 0 days duration.
- θ_{2i} is the negative of the amount of PIQ eventually regained by patient *i*, beginning at the point of recovery from coma. Like θ_{1i} , the coefficient θ_{2i} has a fixed-effect component depending linearly on length of coma, with parameters β_3 and β_4 , and a random-effect component, δ_{2i} .



Figure 12: The asymptotic growth model for recovery of IQ following coma, $Y_{ij} = \theta_{1i} + \theta_{2i}e^{-\theta_{3i}X_{1ij}} + \varepsilon_{ij}$, where Y_{ij} is the PIQ and X_{1ij} is the time post-coma for subject *i* on occasion *j*. The parameter θ_{1i} represents the eventual level of PIQ for subject *i*; $-\theta_{2i}$ is the amount of PIQ recovered by subject *i*; and θ_3 is the rate of recovery for subject *i* (fixed across subjects), with $(\log_e 2)/\theta_3$ representing the time to half-recovery.

- θ_{3i} is the recovery rate for patient *i*, treated as a fixed effect, β_5 , with $(\log_e 2)/\theta_{3i}$ representing the time required to recover half the difference between final and (expected) initial post-coma PIQ (the "half-recovery" time), that is, $-\theta_{2i}/2$. It makes substantive sense to treat the patients' recovery rates as potentially variable—that is as a random effect—but doing so introduces three additional parameters (a variance component and two covariance components) yet (as we will see below) leaves the likelihood essentially unchanged. The very small number of observations per patient produces very little information in the data for estimating patient-specific recovery rates.
- ε_{ij} is the error for patient *i* on occasion *j*.

There are, therefore, four variance-covariance components in this model, $V(\varepsilon_{ij}) = \sigma_{\varepsilon}^2$, $V(\delta_{1i}) = \psi_1^2$, $V(\delta_{2i}) = \psi_2^2$, and $C(\delta_{1i}, \delta_{2i}) = \psi_{12}$. Although the data are longitudinal, there are too few observations per patient to entertain a model with serially correlated errors.

Before fitting this model, we will examine the data, both to determine whether the posited model seems reasonable, and to provide rough guesses for the fixed-effects parameters. As in nonlinear least squares,²⁴. initial guesses of the fixed-effects parameters provide a starting point for the iterative process of maximizing the likelihood in the NLMM.

```
> subjects <- unique(with(Wong, id))
> with(Wong, sum(days > 1000))
```

[1] 40

 $^{^{24}\}mathrm{See}$ the appendix on nonlinear regression



Figure 13: Scatterplot for PIQ versus days since awakening from coma (dayspc). Obervations beyond 1000 days are not shown, and the observations for each patient are connected by gray lines. The heavier black line is for a non-parametric regression smooth.

```
> plot(piq ~ days, xlab="Days Post Coma",
+ ylab="PIQ", xlim=c(0, 1000),
+ data=Wong, subset = days <= 1000)
> for (subject in subjects){
+ with(Wong, lines(days[id==subject], piq[id==subject], col="gray"))
+ }
> with(Wong, lines(lowess(days, piq), lwd=2))
```

Figure 13 is a scatterplot of PIQ versus number of days post-coma, with the observations for each patient connected by lines. Forty of the 331 measurements were taken after 1000 days postcoma, and these are omitted from the graph to allow us to discern more clearly the general pattern of the data. The line on the plot is drawn by lowess. Mixing together the observations from all patients makes the scatterplot difficult to interpret, but, on the other hand, there are too few observations for each patient to establish clear individual trajectories. Nevertheless, the asymptotic growth model is roughly consistent with the general pattern of the data, and the patients for whom there are multiple observations do tend to improve over time.

```
> # selecting first row for each subject:
> Ag.iq <- aggregate(Wong, by=list(id=Wong$id), function(x) x[1])
> summary(Ag.iq)
```

id id days duration sex 13 : 405 : 405 Min. Min. • 0 Female: 43 Min. • Min. 1st Qu.:3710 1st Qu.:3710 1st Qu.: 42 1st Qu.: 1 Male :157 Median :5148 Median :5148 7 Median : 71 Median : :4778 :4778 375 Mean Mean Mean Mean : 14

```
3rd Qu.:5897
                 3rd Qu.:5897
                                 3rd Qu.:
                                           172
                                                  3rd Qu.: 14
 Max.
        :7548
                        :7548
                                 Max.
                                         :11628
                                                          :255
                 Max.
                                                  Max.
      age
                       piq
                                        viq
 Min.
        : 6.51
                  Min.
                         : 50.0
                                   Min.
                                          : 64.0
 1st Qu.:21.76
                  1st Qu.: 74.0
                                   1st Qu.: 83.0
Median :27.25
                  Median : 84.0
                                   Median : 91.0
                                   Mean
Mean
        :32.35
                  Mean
                         : 83.3
                                           : 92.1
 3rd Qu.:40.98
                  3rd Qu.: 93.0
                                   3rd Qu.:101.2
        :80.03
                         :127.0
 Max.
                  Max.
                                   Max.
                                           :131.0
> plot(piq ~ sqrt(duration), data=Ag.iq,
       xlab="Days in Coma (square-root scale)", ylab="Initial PIQ",
+
      axes=FALSE, frame=TRUE, subset = duration <= 100)</pre>
+
> (mod <- lm(piq ~ sqrt(duration), data=Ag.iq, subset = duration <= 100))
Call:
lm(formula = piq ~ sqrt(duration), data = Ag.iq, subset = duration <=</pre>
    100)
Coefficients:
   (Intercept)
                 sqrt(duration)
         88.49
                          -1.93
> abline(mod, lwd=2, lty=2)
>
 with(subset(Ag.iq, duration <= 100),</pre>
       lines(lowess(sqrt(duration), piq), lwd=2))
+
> axis(2)
> axis(1, at=sqrt(c(0, 5, 10, seq(20, 100, by=20))),
+
       labels=c(0, 5, 10, seq(20, 100, by=20)))
```

Figure 14 is a scatterplot of the initial PIQ measurement for each patient against the length of the patient's coma (in days, on the square-root scale). These initial measurements were taken at varying times post-coma and therefore should not be interpreted as the PIQ at time of awakening (i.e., time 0) for each patient. The relationship of initial PIQ to square-root length of coma appears to be reasonably linear.

Figures 13 and 14 also provide a basis for obtaining initial values of the fixed-effects parameters in the mixed model of Equations 10:

- Figure 13 leads us to expect that the average eventual level of recovered IQ will be less than 100, but Figure 14 suggests that the average eventual level for those who spent fewer days in a coma should be somewhat higher; we therefore use the start value $\beta_1^{(0)} = 100$.
- The slope of the least-squares line in Figure 14, relating initial PIQ to the square-root of length of coma, is -1.9, and thus we take $\beta_2^{(0)} = -2$.
- The parameter β_3 represents the negative of the expected eventual gain in PIQ for a patient who spent 0 days in a coma. On the basis of Figure 13, we will guess that such patients start on average at a PIQ of 90 and eventually recover to an average of 100, suggesting the start value $\beta_3^{(0)} = -10$.



Figure 14: Scatterplot of the initial PIQ measurement for each patient (not necessarily taken at day 0) versus the number of days the patient spent in a coma (on the square-root scale). The broken line is a least-squares line, while the solid line is a nonparametric-regression smooth.

- The parameter β_4 represents the change in expected eventual PIQ gain with a 1-unit increase in the length of the coma on the square-root scale. Our examination of the data does not provide a basis for guessing the value of this parameter, and so we will take $\beta_4^{(0)} = 0$.
- Recall that the time to half-recovery is $(\log_e 2)/\beta_5$. From Figure 13, it seems reasonable to guess that the half-recovery time is around 100 days. Thus, $\beta_5^{(0)} = (\log_e 2)/100 = 0.007$.

With these start values for the fixed effects, maximum-likelihood estimation of the model converges rapidly (but REML estimates, not shown, do not converge without simplifying the random effects²⁵):

```
wong.mod.1 <- nlme(pig ~ theta1 + theta2*exp(-theta3*days), data=Wong,</pre>
>
      fixed=list(
+
          theta1 ~ 1 + sqrt(duration),
+
          theta2 ~ 1 + sqrt(duration),
+
          theta3 ~ 1),
+
      random=list(id = list(theta1 ~ 1, theta2 ~ 1)),
+
      start=list(fixed=c(100, -2, -10, 0, 0.007)))
+
> summary(wong.mod.1)
Nonlinear mixed-effects model fit by maximum likelihood
 Model: piq ~ theta1 + theta2 * exp(-theta3 * days)
Data: Wong
   AIC BIC logLik
```

 $^{^{25}}$ We invite the reader to experiment with estimation of the model by REML, adding the argument method="REML" to the calls to nlme.

```
2593 2628 -1288
Random effects:
 Formula: list(theta1 ~ 1, theta2 ~ 1)
Level: id
 Structure: General positive-definite, Log-Cholesky parametrization
                   StdDev Corr
theta1.(Intercept) 13.769 t1.(I)
theta2.(Intercept)
                    2.603 -0.995
Residual
                    6.736
Fixed effects: list(theta1 ~ 1 + sqrt(duration), theta2 ~ 1 + sqrt(duration),
                                                                                     theta3 ~ 1)
                       Value Std.Error DF t-value p-value
theta1.(Intercept)
                       97.09
                                  2.037 127
                                              47.68 0.0000
theta1.sqrt(duration)
                       -1.25
                                  0.480 127
                                              -2.59 0.0107
theta2.(Intercept)
                                              -3.47 0.0007
                      -11.15
                                  3.208 127
theta2.sqrt(duration)
                                              -3.02 0.0031
                       -3.25
                                  1.077 127
theta3
                        0.01
                                               5.00 0.0000
                                  0.002 127
 Correlation:
                      t1.(I) th1.() t2.(I) th2.()
theta1.sqrt(duration) -0.724
theta2.(Intercept)
                      -0.596 0.463
theta2.sqrt(duration) 0.463 -0.455 -0.789
theta3
                      -0.309 0.013 0.092 -0.380
Standardized Within-Group Residuals:
      Min
                 Q1
                           Med
                                      Q3
                                               Max
-3.332401 -0.365697
                     0.008986
                               0.382748 2.303102
Number of Observations: 331
Number of Groups: 200
As mentioned, adding random effects to \theta_3 is ineffective:
> wong.mod.2 <- update(wong.mod.1,</pre>
      random=list(id = list(theta1 ~ 1, theta2 ~ 1, theta3 ~ 1)))
+
> anova(wong.mod.1, wong.mod.2)
           Model df AIC BIC logLik
                                        Test L.Ratio p-value
wong.mod.1
               1
                  9 2593 2628
                               -1288
wong.mod.2
               2 12 2599 2645
                               -1288 1 vs 2 0.001631
                                                             1
```

The call to **nlme** is more or less self-explanatory:

• The right-hand side of the model-formula argument specifies the individual-level, withincluster effects in the model (i.e., the θ s) in the form of an R expression, unlike the right-hand side of a linear-model formula but similar to the formula argument of **nls** for fitting nonlinear models by least squares (as described in the appendix on nonlinear regression).

- Each of the elements in the list associated with the **fixed** argument expresses the dependence of the individual-level effects on the fixed effects, in the form of a linear-model formula. The implied coefficients on the right-hand side of these formulas are the fundamental fixed-effect parameters (i.e., the β s).
- Each of the elements of the list associated with the random argument is a linear-model formula specifying the random effects associated with each of the θ s.
- Start values for the fixed-effect parameters (the β s), required by the nlme function, are given sequentially in the fixed element of the start argument. It is also possible to specify start values for the variance and covariance components, but we've not done that.

The nlme function accomodates much more complex specifications consistent with the NLMM of Equations 9, but its use is reasonably straightforward in our application.

All of the estimated fixed-effects parameters are considerably larger than their standard errors. The estimated correlation between the random effects δ_{1i} and δ_{2i} is very high, however, $r_{\delta_1\delta_2} = -.995$. We might either simplify the model, say by eliminating random effects δ_{2i} from the equation for θ_{2i} , or by reparametrizing the model to reduce the correlation between the random effects.

The estimates of the fixed effects suggest that the average final level of recovered PIQ for individuals in a coma of 0 days duration is $\hat{\beta}_1 = 97.1$. This level declines, as anticipated, with the length of the coma, $\hat{\beta}_2 = -1.25$. On average, patients who spend 0 days in a coma recover $-\hat{\beta}_3 = 11.1$ PIQ points, and the average size of the recovery increases with the length of the coma, $-\hat{\beta}_4 = 3.25$. The estimated half-recovery time is $(\log_e 2)/\hat{\beta}_5 = (\log_e 2)/0.00825 = 84$ days.

We can construct a fixed-effect display (Figure 15), showing how typical PIQ recovery varies as a function of days post coma and length of coma:

```
> newdata <- expand.grid(duration=c(1, 10, 20, 50, 100, 200),
+
                          days=seq(0, 1000, 20))
> newdata$pig <- predict(wong.mod.1, newdata, level=0)</pre>
> plot(piq ~ days, type="n", xlab="Days Post Coma", ylab="Average PIQ",
+
      vlim=c(20, 100), xlim=c(-100, 1000), data=newdata, axes=FALSE, frame=TRUE)
> axis(2)
> axis(4)
> axis(1, at=seq(0, 1000, by=100))
> for (dc in c(1, 10, 20, 50, 100, 200)){
      with(newdata, {
+
          lines(spline(seq(0, 1000, 20), piq[duration == dc]), lwd=2)
+
          text(-25, pig[duration == dc][1], labels=dc, adj=0.9)
+
+
      })
+ }
> text(-100, 95, labels="Length\nof Coma", adj=0)
```

5 Complementary Reading

Much of the material in this appendix is adapted from Fox (2016, Chaps. 23 and 24). A very brief treatment of mixed models may be found in Weisberg (2014, Sec. 7.4). Snijders and Bosker (2012) and Raudenbush and Bryk (2002) are two accessible books that emphasize hierarchical linear and, to a lesser extent, generalized-linear models. Gelman and Hill (2007) develop mixed models in the



Figure 15: Fixed-effect plot of average PIQ by days since recovery from coma and length of coma in days, based on the NLMM fit to the coma-recovery data.

more general context of regression analysis; these authors also discuss Bayesian approaches to mixed models. Stroup (2013) presents a more formal and comprehensive development of generalized linear mixed models, treating other regression models, such as linear models, generalized linear models, and linear mixed-effects models as special cases (and emphasizing **SAS** software for fitting these models).

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