

Introduction to mixed-effects models (for longitudinal data)

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- Try to code along in R! Ask as many questions as possible

Outline

- ① Introduction to longitudinal data
- ② Example: Depression and Imipramin

① Introduction to longitudinal data

Longitudinal data

- Consist of repeated measurements on the same subject taken over time
- Are a frequent use case for mixed-effects models
- Contain time as a predictor: time trends within and between subjects are of interest

```
library("lme4")  
data("sleepstudy")  
?sleepstudy  
str(sleepstudy)  
summary(sleepstudy)  
head(sleepstudy)
```

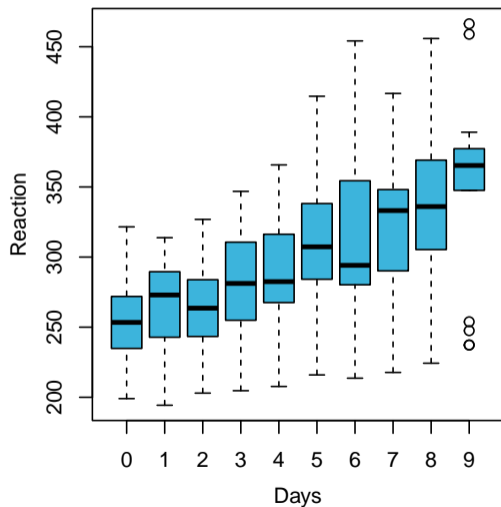
Sleep study

- Average reaction time per day for subjects in a sleep deprivation study
- On day 0, the subjects had their normal amount of sleep
- Starting that night they were restricted to 3 hours of sleep per night
- Observations represent the average reaction time on a series of tests given each day to each subject

A data frame with 180 observations on the following 3 variables

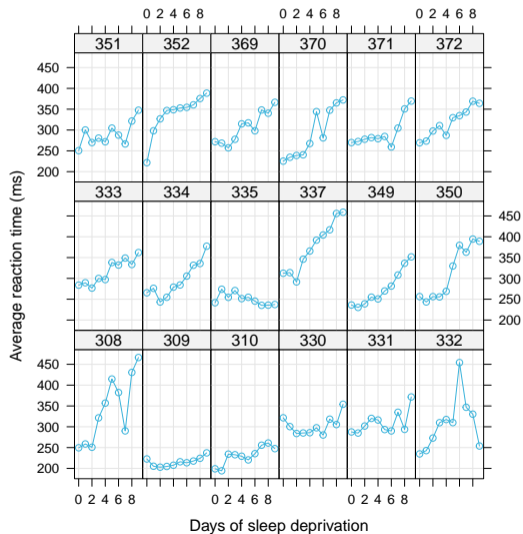
Reaction	Average reaction time (ms)
Days	Number of days of sleep deprivation
Subject	Subject number on which the observation was made

Visualization of data



```
boxplot(Reaction ~ Days, sleepstudy)
```

Visualization of individual data



```
library("lattice")

xyplot(Reaction ~ Days | Subject,
       data = sleepstudy,
       type = c("g", "b"),
       xlab = "Days of sleep deprivation",
       ylab = "Average reaction time (ms)",
       aspect = "xy")
```

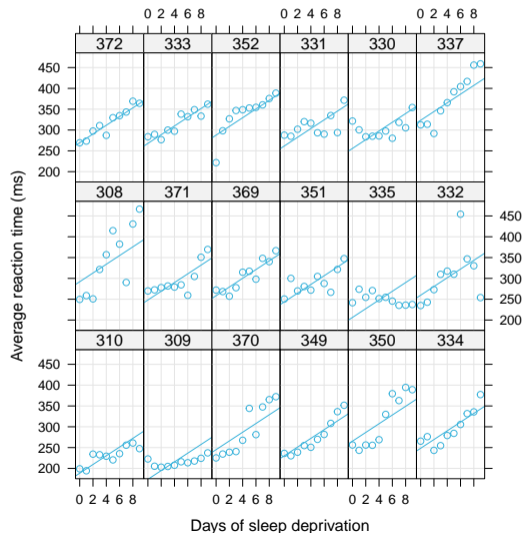
Random intercept model

- The random intercept model adds a random intercept for each subject

$$y_{ij} = \beta_0 + \beta_1 \text{Days}_{ij} + v_{0i} + \varepsilon_i$$

with $v_{0i} \stackrel{iid}{\sim} N(0, \sigma_v^2)$, $\varepsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma_\varepsilon^2)$

- The slope is identical for each subject (and the population)



Fixed and random effects for random intercept model

Subject	Days	Reaction	Fixed		Random	
			Intercept	Slope	SubInt	Resid
308	0	250	251.4	10.5	40.8	-42.6
308	1	259	251.4	10.5	40.8	-44.0
308	2	251	251.4	10.5	40.8	-62.3
⋮	⋮	⋮	⋮	⋮	⋮	⋮
308	8	431	251.4	10.5	40.8	54.7
308	9	466	251.4	10.5	40.8	80.0
309	0	223	251.4	10.5	-77.8	49.2
309	1	205	251.4	10.5	-77.8	21.2
309	2	203	251.4	10.5	-77.8	8.5
⋮	⋮	⋮	⋮	⋮	⋮	⋮
310	0	199	251.4	10.5	-63.1	10.8
310	1	194	251.4	10.5	-63.1	-4.4
310	2	234	251.4	10.5	-63.1	25.1
⋮	⋮	⋮	⋮	⋮	⋮	⋮
					σ_v^2	σ_ε^2

Random slope model

- The random slope model adds a random intercept and a random slope for each subject

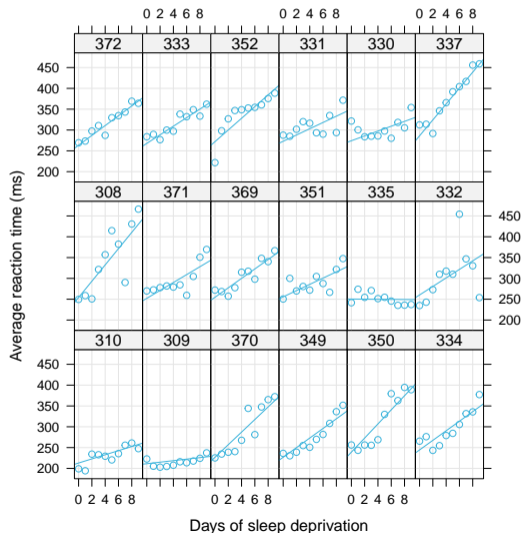
$$y_{ij} = \beta_0 + \beta_1 \text{Days}_{ij} + v_{0i} + v_{1i} \text{Days}_{ij} + \varepsilon_{ij}$$

with

$$\begin{pmatrix} v_{0i} \\ v_{1i} \end{pmatrix} \stackrel{iid}{\sim} N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \boldsymbol{\Sigma}_v = \begin{pmatrix} \sigma_{v_0}^2 & \sigma_{v_0 v_1} \\ \sigma_{v_0 v_1} & \sigma_{v_1}^2 \end{pmatrix} \right)$$

$$\varepsilon_{ij} \stackrel{iid}{\sim} N(0, \sigma_\varepsilon^2)$$

- Individual slopes for each subject

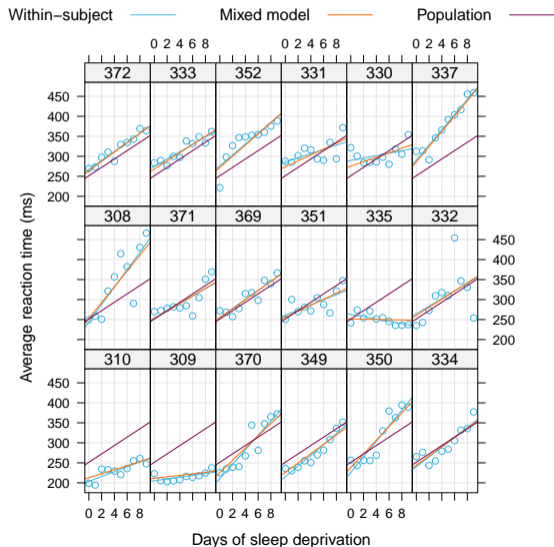


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Subject	Days	Reaction	Fixed		Random		
			Intercept	Slope	SubInt	SubSlp	Resid
308	0	250	251.4	10.5	2.3	9.2	-4.1
308	1	259	251.4	10.5	2.3	9.2	-14.6
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⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮
308	8	431	251.4	10.5	2.3	9.2	19.6
308	9	466	251.4	10.5	2.3	9.2	35.7
309	0	223	251.4	10.5	-40.4	-8.6	11.7
309	1	205	251.4	10.5	-40.4	-8.6	-7.6
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310	0	199	251.4	10.5	-39.0	-5.4	-13.4
310	1	194	251.4	10.5	-39.0	-5.4	-23.1
310	2	234	251.4	10.5	-39.0	-5.4	11.8
⋮	⋮	⋮	⋮	⋮	⋮	⋮	⋮

$$\sigma_{v_0}^2 \quad \sigma_{v_0 v_1} \quad \sigma_{v_1}^2 \quad \sigma_{\epsilon}^2$$

Partial pooling

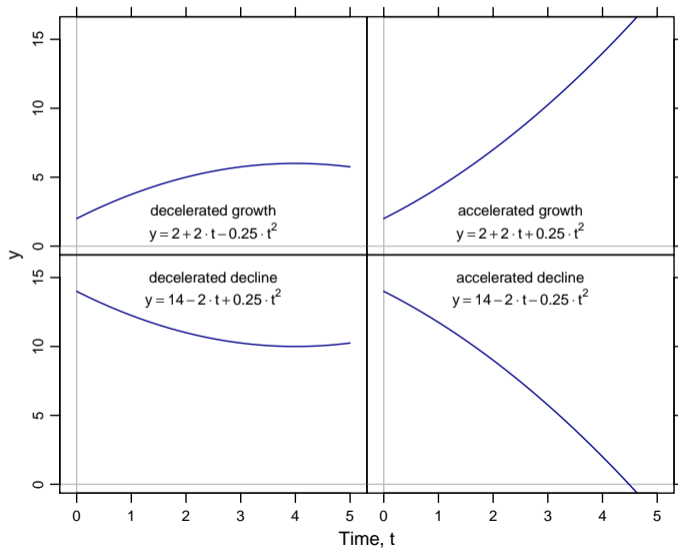


- Within-subject regression line shows regression line fitted to data for each individual
- Population regression line shows fixed effects for mixed-effects model
- Mixed model regression line shows individual regression lines as predicted by mixed-effects models

② Example: Depression and Imipramin

Quadratic time trends

- A lot of times the assumption of a linear time trend is too simple
- Change is not happening unbraked linearly but flattens out



Quadratic time trends

- Quadratic regression model

$$\begin{aligned}y_{ij} &= b_{0i} + b_{1i} t_{ij} + b_{2i} t_{ij}^2 + \varepsilon_{ij} \\ &= b_{0i} + (b_{1i} + b_{2i} t_{ij})t_{ij} + \varepsilon_{ij}\end{aligned}$$

- The linear change depends on time t

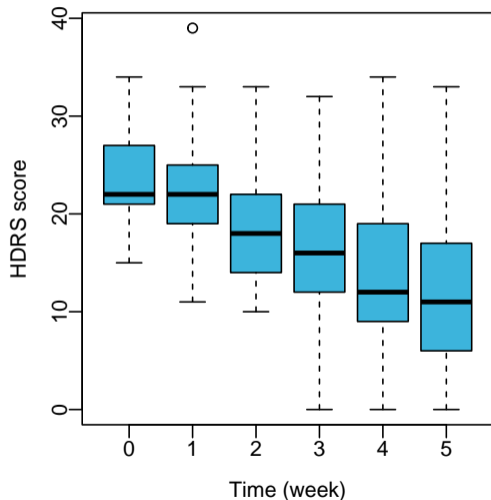
$$\frac{\partial y}{\partial t} = b_{1i} + 2b_{2i} t$$

- The intercept $t = -b_{1i}/(2b_{2i})$ is the point in time when a positive (negative) trend becomes negative (positive)

Depression and Imipramin (Reisby et al., 1977)

- Reisby et al. (1977) studied the effect of Imipramin on 66 inpatients treated for depression
- Depression was measured with the Hamilton depression rating scale (HDRS)
- Additionally, the concentration of Imipramin and its metabolite Desipramin was measured in their blood plasma
- Patients were classified into endogenous and non-endogenous depressed
- Depression was measured weekly for 6 time points; the effect of the antidepressant was observed starting at week 2 for four weeks

Descriptive statistics



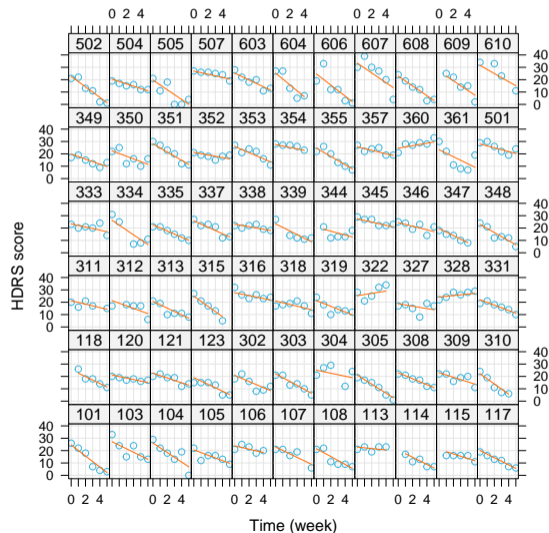
HDRS score

t	W0	W1	W2	W3	W4	W5
M	23.44	21.84	18.31	16.42	13.62	11.95
SD	4.53	4.70	5.49	6.42	6.97	7.22
n	61	63	65	65	63	58

Empirical correlation matrix of HDRS score

	W0	W1	W2	W3	W4	W5
Week 0	1	.49	.41	.33	.23	.18
Week 1	.49	1	.49	.41	.31	.22
Week 2	.41	.49	1	.74	.67	.46
Week 3	.33	.41	.74	1	.82	.57
Week 4	.23	.31	.67	.82	1	.65
Week 5	.18	.22	.46	.57	.65	1

Predictions random slope model



$$y_{ij} = \beta_0 + \beta_1 \text{time} + v_{0i} + v_{1i} \text{time} + \varepsilon_{ij}$$

with

$$\begin{pmatrix} v_{0i} \\ v_{1i} \end{pmatrix} \text{ iid } N \left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \boldsymbol{\Sigma}_v = \begin{pmatrix} \sigma_{v_0}^2 & \sigma_{v_0 v_1} \\ \sigma_{v_0 v_1} & \sigma_{v_1}^2 \end{pmatrix} \right)$$

$$\varepsilon_{ij} \text{ iid } N(0, \sigma^2 \mathbf{I}_{n_i})$$

Exercise

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```
dat      <- read.table("data/reisby.txt", header = TRUE)
dat$id   <- factor(dat$id)
dat$diag <- factor(dat$diag, levels = c("nonen", "endog"))
dat      <- na.omit(dat)      # drop missing values
```

Model with quadratic trend

- Model with quadratic individual and quadratic group trend

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 t_{ij}^2 + v_{0i} + v_1 t_{ij} + v_2 t_{ij}^2 + \varepsilon_{ij}$$

with

$$\begin{pmatrix} v_{0i} \\ v_{1i} \\ v_{2i} \end{pmatrix} \stackrel{iid}{\sim} N \left(\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_{v_0}^2 & \sigma_{v_0 v_1} & \sigma_{v_0 v_2} \\ \sigma_{v_0 v_1} & \sigma_{v_1}^2 & \sigma_{v_1 v_2} \\ \sigma_{v_0 v_2} & \sigma_{v_1 v_2} & \sigma_{v_2}^2 \end{pmatrix} \right)$$

$$\varepsilon_i \stackrel{iid}{\sim} N(\mathbf{0}, \sigma^2 \mathbf{I}_{n_i})$$

Model with quadratic trend

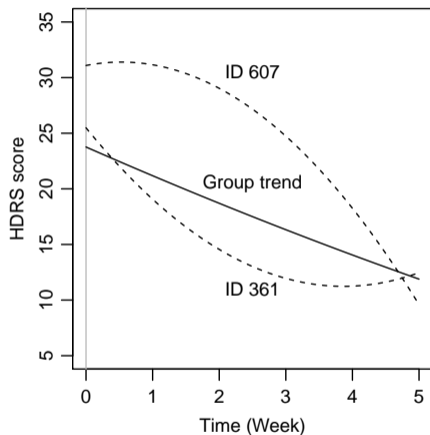
```
library("lme4")

# random intercept model
lme1 <- lmer(hamd ~ week + (1 | id), data = dat, REML = FALSE)

# random slope model
lme2 <- lmer(hamd ~ week + (week | id), data = dat, REML = FALSE)

# model with quadratic time trend
lme3 <- lmer(hamd ~ week + I(week^2) + (week + I(week^2) | id),
             data = dat, REML = FALSE)
```

Model predictions

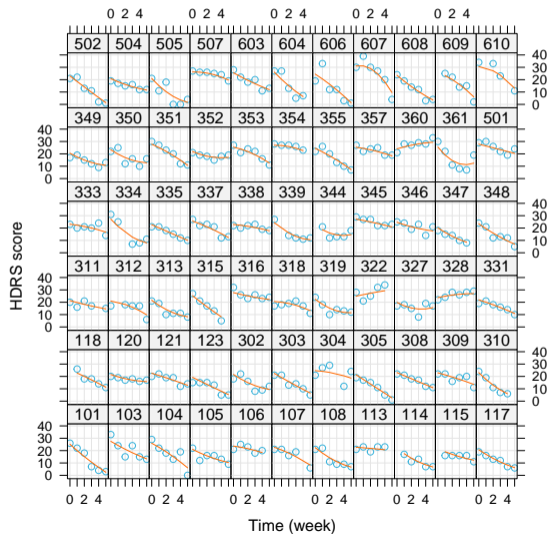


- Averaged over persons an approximately linear trend is obtained, $\hat{\beta}_1 = -2.63$, $\hat{\beta}_2 = 0.05$
- Some of the predicted individual trends are strongly nonlinear

- Test against a model without individual quadratic trends

$$H_0: \sigma_{v_2}^2 = \sigma_{v_0v_2} = \sigma_{v_1v_2} = 0 \quad G^2(3) = 10.98, p = .012$$

Model predictions



```
xyplot(
  hamd + predict(lme3)
    ~ week | id,
  data = dat,
  type = c("p", "l", "g"),
  pch = 16,
  distribute.type = TRUE,
  ylab = "HDRS score",
  xlab = "Time (Week)")
```

Centering variables

- If multiples of the time variables (t , t^2 , t^3 , etc.) are entered into the regression equation, multicollinearity can become a problem
- For example, $t = 0, 1, 2, 3$ and $t^2 = 0, 1, 4, 9$ correlate almost perfectly
- By centering the variables, this problem can be diminished:
 $(t - \bar{t}) = -1.5, -0.5, 0.5, 1.5$ and $(t - \bar{t})^2 = 2.25, 0.25, 0.25, 2.25$ are uncorrelated
- By centering variables the interpretation of the intercept in a linear model changes:
 - Uncentered intercepts represent the difference to the first time point ($t = 0$)
 - Centered intercepts represent the difference after half of the time

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- Center time

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- Refit the model with quadratic effects when time is centered
- Which parameters change?
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 - How do the variance components for the random effects change?
- *Why* do the variance components for the random effects change?

Analysis with centered time variable

```
dat$week_c <- dat$week - mean(dat$week)
cor(dat$week, dat$week^2)      # 0.96
cor(dat$week_c, dat$week_c^2)  # 0.01

# random slope model
lme2c <- lmer(hamd ~ week_c + (week_c | id), data = dat, REML = FALSE)

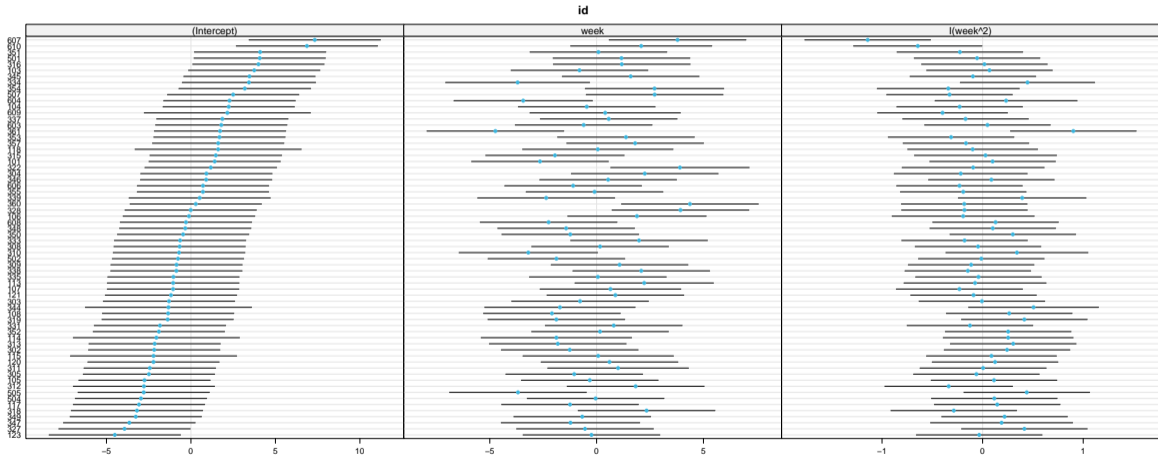
# model with quadratic time trend
lme3c <- lmer(hamd ~ week_c + I(week_c^2) + (week_c + I(week_c^2) | id),
              data = dat, REML = FALSE)
```

Investigating random effects structure

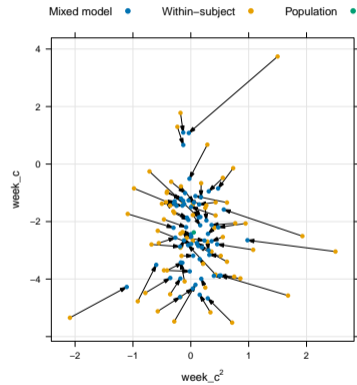
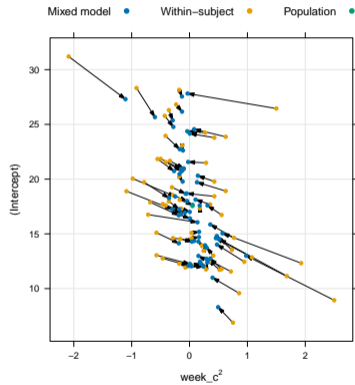
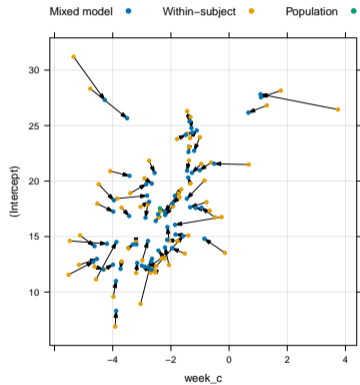
- In order to get a better understanding of the necessary random effects it might be a good idea to take a closer look at them
- Two plots often used are the so-called caterpillar and shrinkage plots
- Play around with different models and compare how, e. g., the caterpillar plots change with and without covariances in the model!

```
library("lattice")  
dotplot(ranef(lme3), scales = list( x = list(relation = "free")))$id
```

Caterpillar plot



Shrinkage plots



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- You can send questions to me and even make an appointment with me to go over your solution

References

- Alday, P., Kliegl, R., & Bates, D. (2025). *Embrace uncertainty – Mixed-effects models with Julia*. <https://embraceuncertaintybook.com/>
- Bates, D. (2010). *lme4: Mixed-effects modeling with R (book draft)*. <https://lme4.r-forge.r-project.org/>
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